이학박사 학위논문

Design, Synthesis and Application of Chiral Diamine-based Building Blocks via Diaza-Cope Rearrangement (DCR)

다이아자 코우프 자리바꿈 반응기법에 근거한 키랄 다이아민 기반의 구조체들의 설계, 합성 및 응용

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CONTENTS

Abstract 5

List of Figures 8

List of Schemes 9

List of Tables 10

Background 11

Chapter I.

Synthesis of Chiral *trans*-3-Arylpiperazine-2-carboxylic Acid Derivatives

1. Introduction 24

2. Result and Discussion 26

3. Conclusion 33

4. Experimental 33

Chapter II.

Stereospecific Synthesis of γ,δ-Diamino Esters

1. Introduction **48**

2. Result and Discussion **49**

3. Conclusion **55**

4. Experimental **56**

Chapter III.

Stereospecific Synthesis of a Twinned Alanine Ester

1. Introduction **67**

2. Result and Discussion **69**

3. Conclusion **76**

4. Experimental **77**

Chapter IV.

Sugar as Chiral Derivatizing Agent for the Determination of the Enantiopurity of Vicinal Diamines

1. Introduction **81**

2. Result and Discussion **82**

3. Conclusion **86**

4. Experimental **87**

References **91**

Appendix A (NMR spectra) **105**

Appendix B (HPLC spectra) **143**

Appendix C (Computational data) **168**

Appendix D (Crystal data) **173**

국문초록 **205**

Abstract

Design and Synthesis and Application of Chiral Diamine-based Building Blocks via Diaza-Cope Rearrangement

Much interest has been concentrated in the vininal diamine chemistry since many metal-based catalyst and organocatalysts as well as biologically active molecules containing the diamine structure have been synthesized. Diaza-Cope rearrangement (DCR) is a versatile tool for providing a variety of symmetrically-substituted as well as non-symmetrically-substituted chiral vicinal diamines. As the DCR route was introduced, it has rendered the structural tuning and thus electronic diversification of diamino functionality at ease so that many chemists could discover and develop new catalysts and applications owing to the simplicity and effectiveness of the rearrangement. However, use of the DCR for the construction of chiral building blocks for physiologically active molecules or peptidomimetic structures has not been as actively pursued as for catalysts.

The DCR allows for stereospecific synthesis of chiral vicinal diamines through the rearrangement of diimines prepared from 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (*hpen*) and aldehydes. With a broad perspective, the chiral nonsymmetrical 1,2-disubstituted vicinal diamines could serve as suitable intermediates for the preparation of many physiologically active compounds. Using the *hpen* as a starting material, a number of useful chiral molecules containing diamine functionality can be synthesized.

Piperazine-2-carboxylic acid has been utilized as an amino acid surrogate in many biologically active compounds. In Chapter 1, the development of an

efficient route for enantiopure *trans*-3-arylpiperazine-2-carboxylic acid derivatives is described though the DCR process. A complete transfer of stereochemical integrity was observed for the transformation. Piperazine ring formation from the chiral 1,2-ethylenediamine derivatives using diphenylvinylsulfonium triflate, followed by oxidation using $Ru(III)Cl_3 \cdot H_2O$ in the presence of $NaIO_4$ provided the desired enantiopure *trans*-3-arylpiperazine-2-carboxylic acid derivatives.

The rearrangement also allows us to prepare γ,δ-diamino acids, which may be useful for the synthesis of Tamiflu-type antiviral agents as well as various biologically active compounds. In Chapter II, we report the one-pot reaction for the synthesis of γ,δ-diimino esters with two adjacent chiral centers in enantiomerically pure form through DCR of diimines formed from (*R,R*)-*hpen* and aldehydes. DFT computation provides interesting understanding into the stereospecific rearrangement reaction. The crystal structure of the product diimine formed from the reaction of (*R,R*)-*hpen* and 2,6-dichlorobenzaldehyde shows that the reaction gives the product in *S,S* configuration.

Preparation of vicinal quaternary carbon centers containing vicinal diamines is synthetically challenging task. In Chapter III, we show that the synthesis of a twinned alanine derivative is efficiently accomplished through the DCR method. Reaction between (*R,R*)-*hpen* and methyl pyruvate gives the diaza-Cope rearrangement product with good yield and excellent stereospecificity. The product containing two chiral quaternary carbon centers on vicinal position is characterized by high performance liquid chromatography (HPLC) and X-ray crystallography. DFT computation helps the understanding of why the diaza-Cope rearrangement takes place readily with methyl pyruvate but not with other ketones like acetone and substituted acetophenones.

The structural prevalence of chiral vicinal diamines as versatile chiral building blocks has led to an intense demand of useful tools to simply and

inexpensively determine the enantiomeric excess (ee) of the diamine molecules. In Chapter IV, we find that use of sugar molecules such as ribose and arabinose as chiral derivatizing agents is quite efficient in providing good analytical tool to determine the enantiopurities of C_2-symmetric vicinal diamines. In this protocol, sugars or diamines do not need to be protected or modified in advance.

Key words: Diaza-Cope Rearrangement/ HPEN / Stereospecific Synthesis / Chiral *trans*-3-Arylpiperazine-2-carboxylic Acids / Chiral γ,δ-Diamino Acids / Twinned Alanine Ester / Sugar / Chiral Derivatizing Agent

List of Figures

Figure 1. Diamine-based Bioactive Molecules.

Figure 2. Diamine-based Transition Metal Catalysts and Organocatalysts.

Figure 3. Possible Transition States for the Chirality Transfer Through DCR.

Figure 4. Various Applications of *hpen* in Transition Metal Catalysts and Organocatalysts.

Figure 5. Other Applications of DCR.

Figure I-1. Compounds Containing Chiral Piperazine-2-carboxylic Acid Derivatives.

Figure II-1. Compounds Containing γ,δ-Diamino Acid Core.

Figure II-2. Crystal Structure of Diimine **3d**.

Figure III-1. Applications of Diamines Derived from *hpen.*

Figure III-2. Crystal Structure of Chiral Diimine **3.**

Figure III-3. Transition State of **4**.

Figure IV-1. Expansion of the Aminal Proton Region of ^{1}H NMR Enantiomerically Mixed *dpen* and D-(-)-ribose.

Figure IV-2. The Degree of Linearity between NMR and Chiral HPLC Analyses.

List of Schemes

Scheme 1. Catalytic Mechanism for the Transamination Reaction of PLP-Dependent Coenzymes.

Scheme 2. Synthesis of Chiral C_2-Symmetric Vicinal Diamines via DCR.

Scheme 3. Stereospecific Synthesis of α-Substituted *syn*-α,β-Diamino Esters.

Scheme I-1. Stereospecific Synthesis of Diimine via DCR

Scheme I-2. Synthesis of Enantiopure *trans*-3-Arylpiperazine-2-carboxylic Acids

Scheme II-1. Stereospecific Synthesis of γ,δ-Diimino Ester Derivatives.

Scheme II-2. Calculated Activation Enthalpies for the DCR.

Scheme II-3. Energy Profile for the DCR Process of Aryl and Alkyl Diimines Substituted with Congujugated Ester.

Scheme II-4. Hydrolysis of Diimines.

Scheme III-1. Previously Reported Synthetic Methods of Twinned Alanine Derivatives.

Scheme III-2. Stereospecific Synthesis of Twinned Alanine Ester.

Scheme III-3. Comparison of Energy Barrier Following *p*-Substituents on Acetophenones.

Scheme III-4. Comparison of Diimine Formation From *hpen* with Acetone/Methyl Pyruvate.

Scheme IV-1. Imidazolidines from Diamines and Sugars.

List of Tables

Table I-1. Stereospecific Synthesis of Chiral Nonsymmetrical Disubstituted Diimines.

Table I-2. Synthesis of *N*-Ns-Protected Vicinal Diamines.

Table I-3. Annulation of Diamines with Various Protecting Groups.

Table II-1. Synthesis of γ,δ-Diamino Ester Derivatives.

Table IV-1. Chemical Shift Differences (Δδ) in the 400 MHz ^{1}H NMR Spectra in MeOH-d_4.

Table IV-2. Comparison of NMR Spectra and HPLC Analysis.

Background

Vicinal diamine is a useful building block for biologically active compounds and commercially available drugs and drug candidate molecules. The vicinal diamine functionality is often embedded in bioactive molecules through their own structure as well as other moieties such as imidazoldine, piperazine, piperidine, β-lactam and γ,δ-diamino acid (Figure 1).[1] For example, 1,2-diaminocylohexane (*dach*) moiety was used to synthesize Oxaliplatin (**1**), an anticancer drug,[2] and U-50,488 (**2**), a highly selective *κ*-opioid agonist.[3]

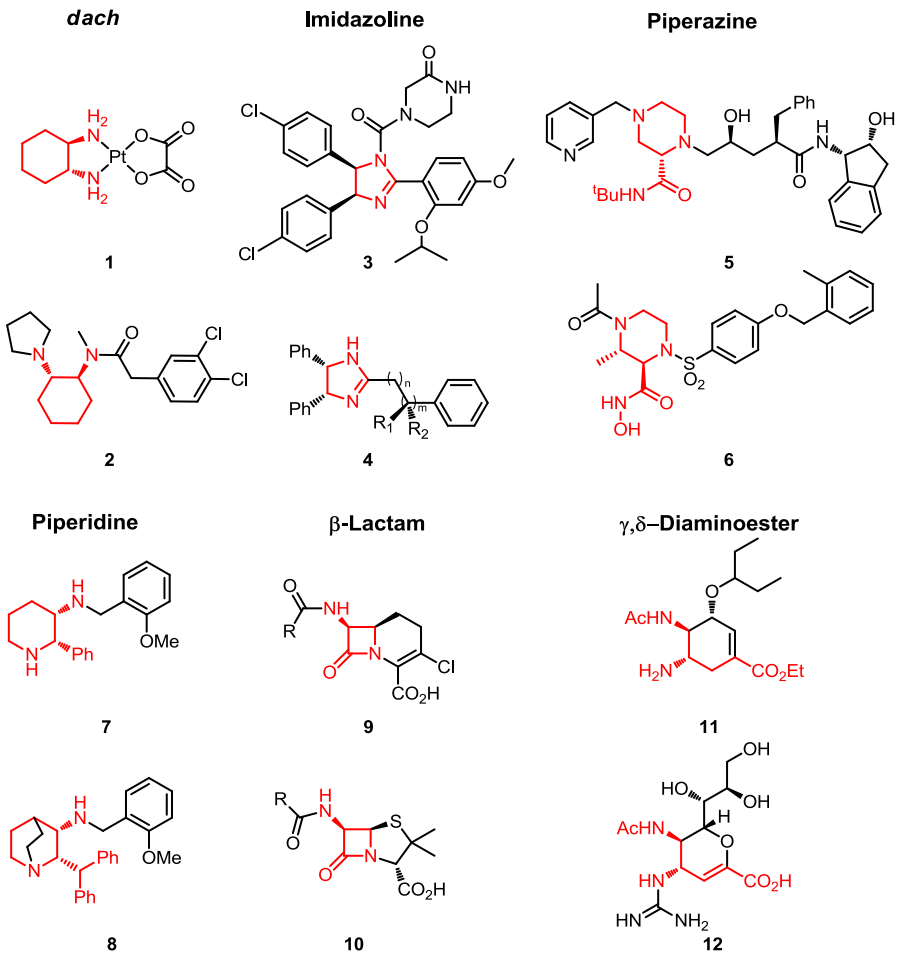


Figure 1. Diamine-based Bioactive Molecules.

Among others, examples of imidazolidine-type diamines such as Nutlin-3 (**3**), an anticancer drug[4] and 4,5-diaryl imidazoline derivatives (**4**), a $P2X_7$ receptor antagonist,[5] have been reported, both of which contain *meso*-vicinal diamine structures. Molecules embedding heterocyclic structures including piperazine and piperidine exhibit various biological activities such as inhibition of HIV protease (Indinavir, **5**),[6] inhibition of MMP-13, TNF-α converting enzyme (**6**),[7] CP-99,994 (**7**) and CP-96,345 (**8**) showing antidepressant, anxiolytic antiemetic properties as a NK_1 receptor antagonists,[8] β-Lactam antibiotics such

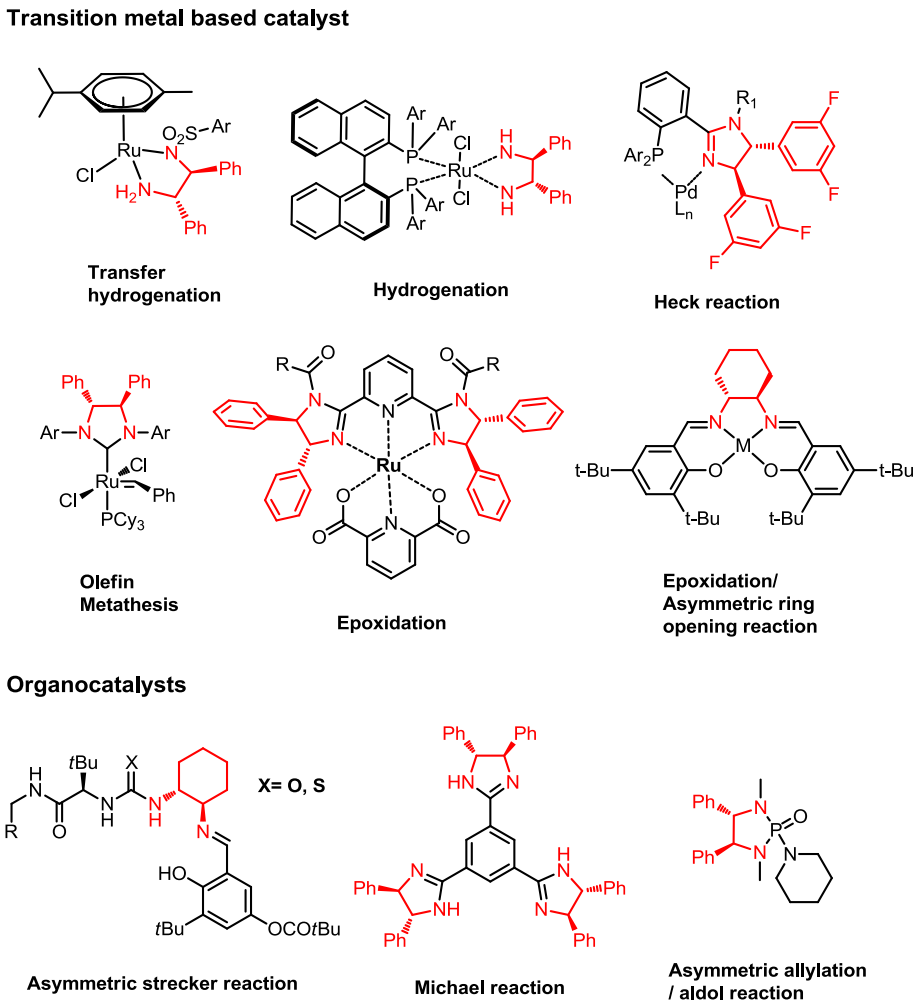
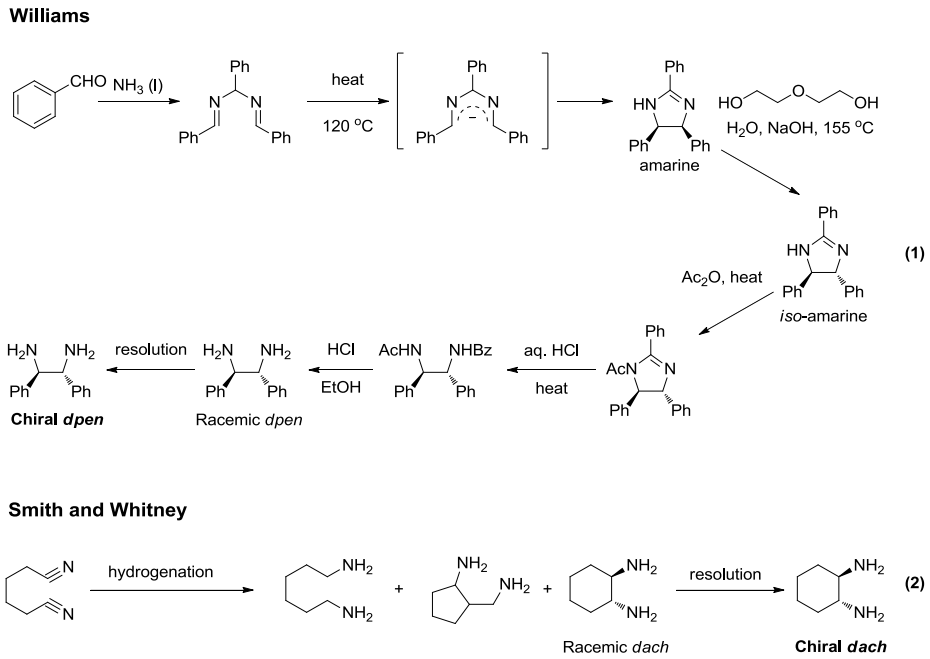


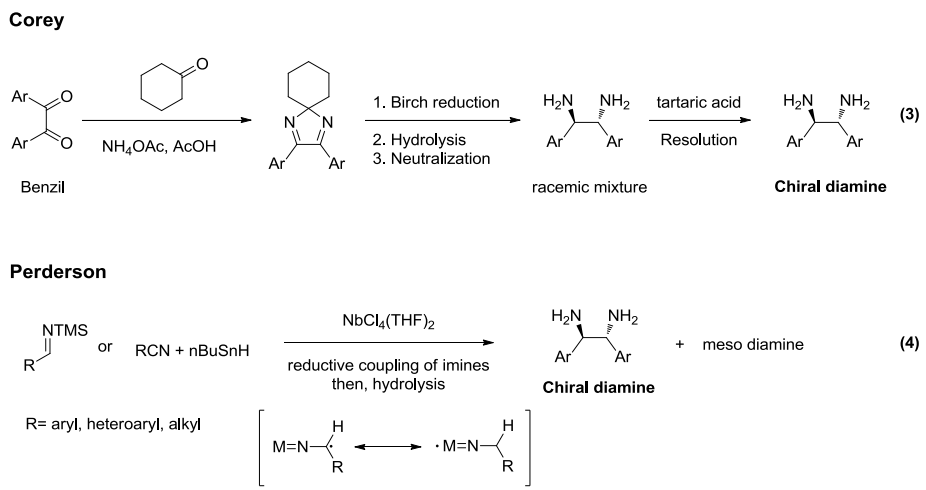
Figure 2. Diamine-Based Transition Metal Catalysts and Organocatalysts.

as penicillins (**9**)[9] and loracarbef (**10**)[10] are used in the treatment of bacterial infection. Oseltamivir (**11**) and Zanamivir (**12**) exhibit potent antiviral activity and have γ,δ-diamino acid functionality in their skeleton. They serve as potent lead compounds for developing neuraminidase inhibitors.[11]

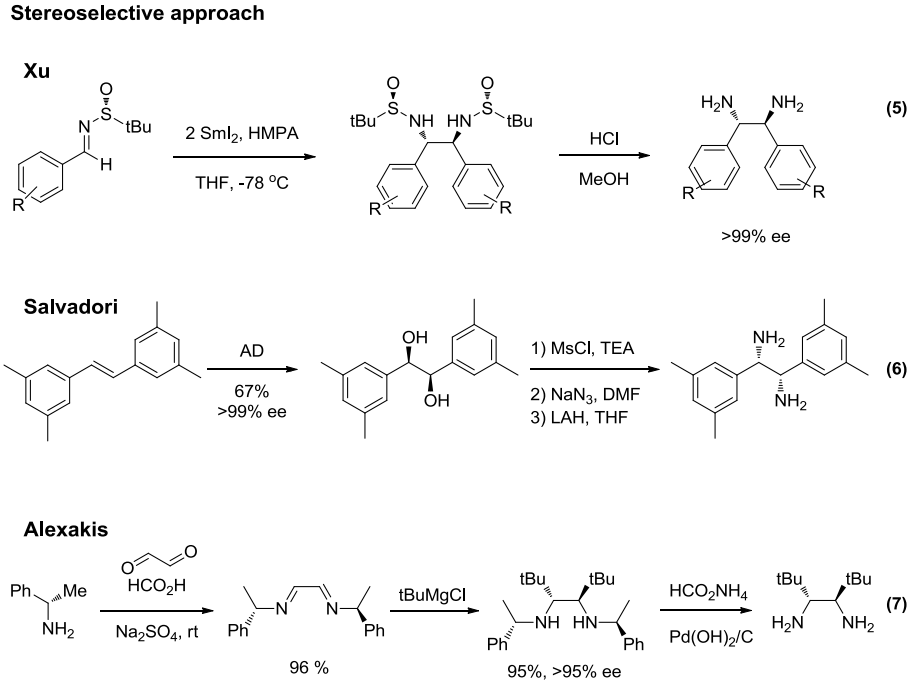
Vicinal diamine-based molecules are also crucial components in the design and synthesis of various chiral catalysts, and these molecules have been used in stereoselective organic synthesis, for example as ligands for transition metal-based catalyst and organocatalysts (Figure 2). Examples of reactions utilizing chiral diamines as the ligands of transition metal-based catalysts include various reactions such as transfer hydrogenation,[12] hydrogenation,[13] asymmetric Heck reaction,[14] olefin metathesis,[15] epoxidation[16] and asymmetric ring opening reaction.[17] Also, organocatalysts with vicinal diamino functionalities have been used for asymmetric Strecker reaction,[18] Lewis base catalyzed allylation and aldol reaction[19] and Michael reaction.[20]



The production of 1,2-diphenyl-1,2-diaminoethane (*dpen*, Eq. 1)[21] and 1,2-diaminocyclohexane (*dach*, Eq. 2)[22] have been of considerable interest for the construction of a large number of metal-based catalysts and organocatalysts as well as biologically active therapeutic agents over several decades as previously shown. However, individual synthesis of a wide variety of diamine structures was required to develop and discover better catalysts and bioactive molecules. For this reason, previous syntheses of C_2-symmetric chiral vicinal diamines having aryl or alkyl substituents are highlighted herein. In 1995, Corey *et al.*[23] reported a synthetic route for chiral 1,2-diaryl-1,2-diaminoethane (Eq. 3). They used aryl-substituted benzil analogs as a starting material to prepare corresponding imidazole intermediate, followed by Birch reduction and hydrolysis. The obtained products were neutralized, then resolved through the use of tartaric acid to give (*R*,*R*)- and (*S*,*S*)-1,2-diaryl-1,2-diaminoethane. Pedersen and coworkers[24] showed that chiral vicinal diamines could be prepared through the coupling of nitriles or *N*-(trimethylsilyl)imines mediated by $NbCl_4(THF)_2$ (Eq. 4). The synthetic method is originated from the resonance structure of a simple d^1 *N*-metal imine derivative and corresponding radical species are then dimerized, follow-



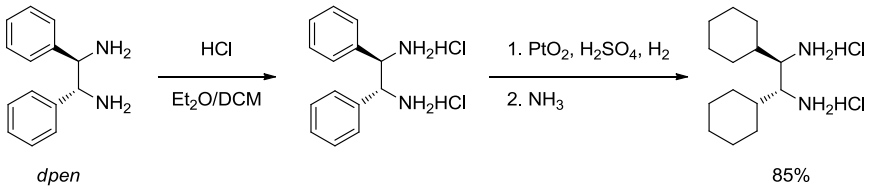
ed by hydrolysis to yield racemic aryl or alkyl substituted vicinal diaimines. Both methods are among the most used pathways for the synthesis of racemic vicinal diamines, however, the racemic mixture needs to be separated into two enantiomers through chiral resolution, which often result in low overall yields.



There have been diverse approaches to synthesize chiral vicinal diamines directly. Xu and coworkers[25] have discovered highly diastereoselective and enantioselective synthesis of C_2-symmetric vicinal diamines through efficient reductive homocoupling of chiral *N*-tert-butanesulfinylimines in the presence of SmI_2 and HMPA (Eq. 5). This method gives chiral *dpen* derivatives in excellent enantioselectivity in varying yields. Salvadori and coworkers[26] have developed a four step route using *trans*-stilbene as starting material, which is easily converted to enantiopure diol by Sharpless asymmetric dihydroxylation (AD) (Eq. 6). Tosylation of the chiral diol and subsequent double displacement by sodium azide provides azide intermediate, which is then reduced with LAH to provide 1,2-diphenyl-1,2-diaminoethane in >99 % ee.

Alexakis' group[27] introduced a diastereoselective synthesis of alkyl substituted vicinal diamines through the addition of *t*-butylmagnesium chloride to a chiral bis-imine derivative prepared from chiral methylbenzylamine and glyoxal (Eq. 7).

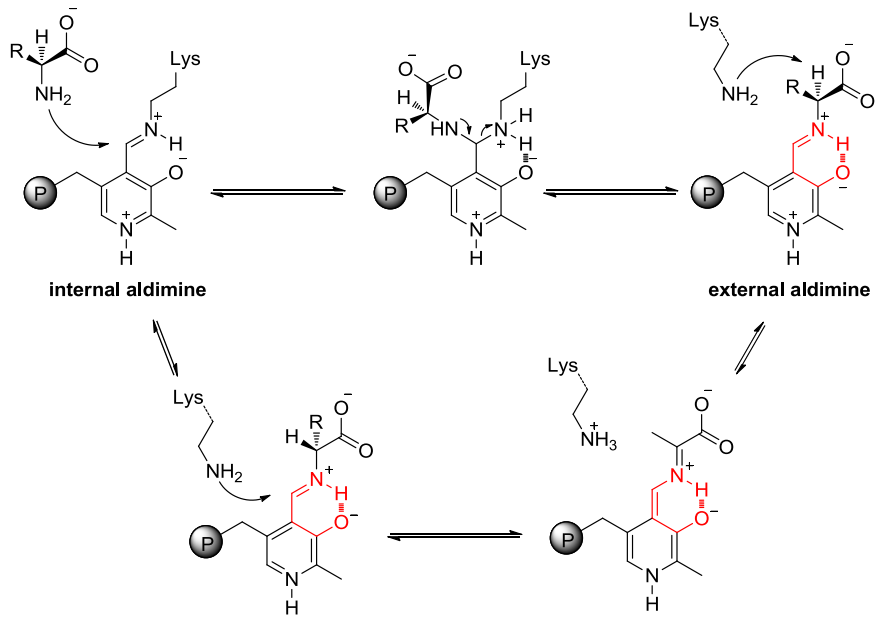
Chiral dpen was also used as a starting material for chiral diamine. Chiral 1,2-dicyclohexylethylenediamines were synthesized by hydrogenation of *dpen* hydrochloride in presence of platinum(IV) oxide (Eq. 8).[28]



(8)

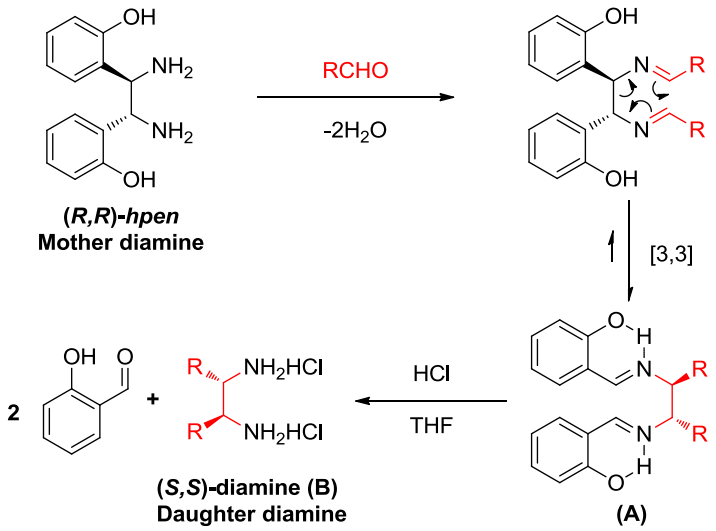
As described previously, various approaches have been investigated to devise efficient synthetic methods for chiral vicinal diamines. However, for developing better catalysts and improving biological activities of drugs and drug candidates, it has been a challenge to develop general and yet efficient synthetic way to a wide variety of enantiomerically pure vicinal diamines. Recently, Chin and coworkers[29] have developed a useful method for synthesizing chiral vicinal diamines through DCR. The rearrangement reaction was first reported in 1973 by Vögtle and Goldschmitt for the synthesis of a wide range of *meso*-1,2-diamines.[30] Chin and coworkers reported that the completion of the rearrangement reaction is derived from resonance assisted hydrogen bonding (RAHB) that dramatically shift the reaction equilibrium to one side.[31] The concept of resonance assisted hydrogen bonding has also played an important role in endogenous enzymatic reactions that catalyze a large number of biochemical reactions, including the biosynthesis of amino acids by the pyridoxal-5'-phosphate-dependent enzymes (PLP enzymes) (Scheme 1).[32] As exemplified in Scheme 1, the

transamination converting an internal aldimine into an external one is thermodynamically favorable (-12 kcal/mol) and stabilized by RAHB. Based on the importance of the H-bond effect in biosystem, Gilli *et al.*[33] investigated that RAHB is a model of synergistic interplay between H-bond strengthening and π-delocalization. This study explained the abnormally strong intramolecular hydrogen bond induced by resonance effect in various molecules using IR, X-ray and DFT calculation.



Scheme 1. Catalytic Mechanism for the Transamination Reaction of PLP-Dependent Coenzymes (P represents the phosphate group).

These seminal works on the DCR by Vögtle *et al*. and on the RAHB by Gilli *et al.* have led to the development of RAHB-directed DCR. Since Chin's group introduced the new synthetic method using the DCR starting from (*R,R*)/(*S,S*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (*hpen*), which is called 'mother diamine', a variety of C_2-symmetric aryl or alkyl substituted vicinal diamines with exceptionally high enantiopurities have been synthesized (Scheme 2).



R_1=R_2= Aryl

Ar	Yield (B) (%)	ee (%)	Ar	Yield (B) (%)	ee (%)
C_6F_5	77	>99	4-$MeOC_6H_4$	78	>99
4-$O_2NC_6H_4$	73		4-HOC_6H_4	74	
4-$MeO_2CC_6H_4$	87		4-$Me_2NCC_6H_4$	69	
4-FC_6H_4	87		2-$MeOC_6H_4$	79	
4-ClC_6H_4	78		2-ClC_6H_4	81	
4-$F_3CC_6H_4$	80		2-$MeCC_6H_4$	75	
4-NCC_6H_4	85		1-Naphthyl	78	
4-$AcHNC_6H_4$	90		2,4,6-triMeOC_6H_2	79	

R_1=R_2= Alkyl

R	Yield (A) (%)	ee (%)		Yield (B) (%)	ee (%)
isopropyl	85	>99	⟶	91	>99
cyclohexyl	80			95	
cyclopropyl	73			90	
ethyl	71			94	

Scheme 2. Synthesis of Chiral C_2-symmetric Vicinal Diamines via DCR.

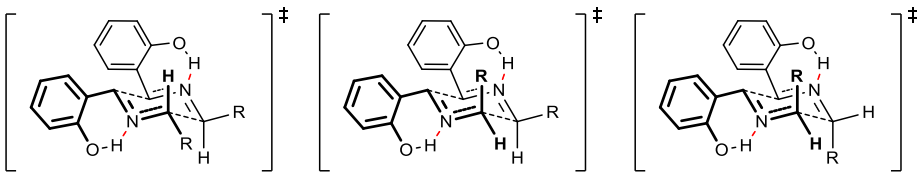
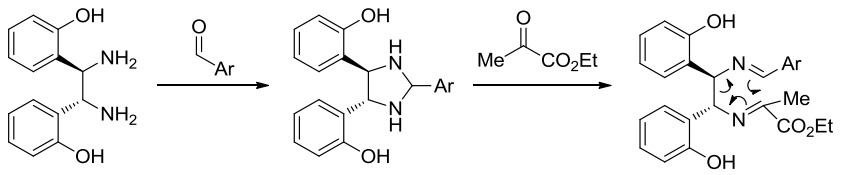


Figure 3. Possible Transition States for the Chirality Transfer Through DCR.

In case of the synthesis of aryl-substituted diamines,[34] addition of 2 equiv of aryl aldehyde to (*R,R*)-*hpen* in the presence of solvent such ethanol or dimethylsulfoxide (DMSO) results in the formation of the corresponding initial diimines, followed by efficient [3,3]-sigmatropic rearrangement. The product diimines are then hydrolyzed to furnish the desired product diamines in acidic conditions. In case of the synthesis for alkyl substituted diamines,[35] refluxing the reaction mixture for 24 h in toluene instead of EtOH or DMSO was required. The product diimines are then hydrolyzed by acidic cleavage to provide the desired product diamines. All the diamines obtained thus far exhibit >99% enantiomeric purities.

To gain some insights into the origin of the chirality transfer, three possible chair-like transition states are considered where substituents are located on different positions in each transition state (Figure 3).[29a] Among them, transition state A is considered to be the most stable because all four substituents are in the equatorial positions with the smallest 1,3-diaxial interaction in six membered conformation. Therefore, the product diimine of the reaction converged into one enantiomer resulting in the stereospecific transfer of the stereochemistry.



Ar	Yield (%)	de (%)	ee (%)
Ph	60	>97	>98
4-FC_6H_4	65	>97	>98
C_6F_5	65	>97	>98
4-HOC_6H_4	58	>97	>98
2-furanyl	67	>97	>98
N-tosyl-3-indolyl	52	>97	>97

Scheme 3. Stereospecific Synthesis of α-Substituted *syn*-α,β-Diamino Esters.

The Chin group also reported the stereospecific synthesis of α-substituted *syn*-α,β-diamino esters, which are used as versatile building blocks for natural amino acid analogues and enzyme inhibitors through DCR with complete transfer of chirality derived from (*R*,*R*)-*hpen* (Scheme 3).[36] This meaningful study showed that the rearrangement is also utilized for synthesizing chiral vicinal diamines possessing a quaternary chiral carbon center.

With the ease and effectiveness of the DCR with ready availability of *hpen*, wide ranging applications of the method have been published including tuning of the reactivity and stereoselectivity of transition metal based catalysts and organocatalysts (Figure 4).

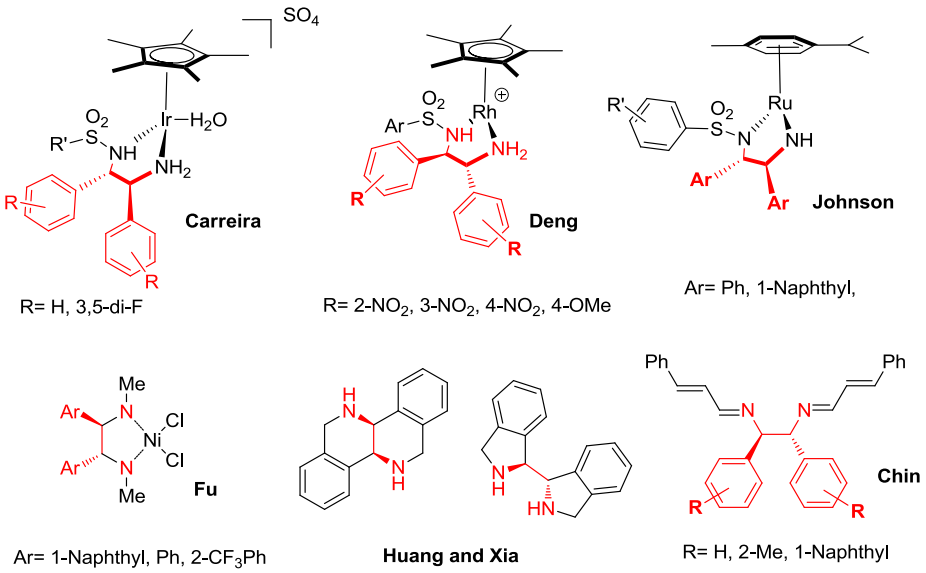


Figure 4. Various Applications of *hpen* in Transition Metal Catalysts and Organocatalysts.

Carreira[37] and Deng[38] developed Ir(III) and Ru(II) complex catalysts with tuning of diamine backbones that were synthesized from chiral *hpen*. These catalysts were then optimized for the transfer hydrogenation reaction of

substituted nitroalkenes and acetophenones. Johnson[39] also used structural variants of vicinal diamines to give the diversity in the catalyst, thus enhancing the selectivity and the reactivity of catalysts for dynamic kinetic resolution of α-keto esters. Additionally, Fu[40] developed the diamines based Ni(II) complex for asymmetric Suzuki coupling reaction and asymmetric Negishi α-alkylation. The catalysts have been optimized by tuning chiral diamine backbones from *hpen*. Huang and Xia[41] designed a new and efficient chiral bisisoindoline and its isomer with rigid backbones. These structures were prepared using the rearrangement reaction starting from *hpen* and were employed as a ligand in the Ni(II) catalyzed Michael addition reaction of malonates to conjugated nitroalkenes. For organocatalyst, Chin[42] introduced the substrate-directed reaction for synthesizing Warfarin using C_2-symmetric vicinal diamines that were tuned by changing substituents on the diamine-based skeleton.

Other applications have been developed over various areas in chemistry. New Co(II)-salen based fluorescent sensors for selectively detecting cyanide

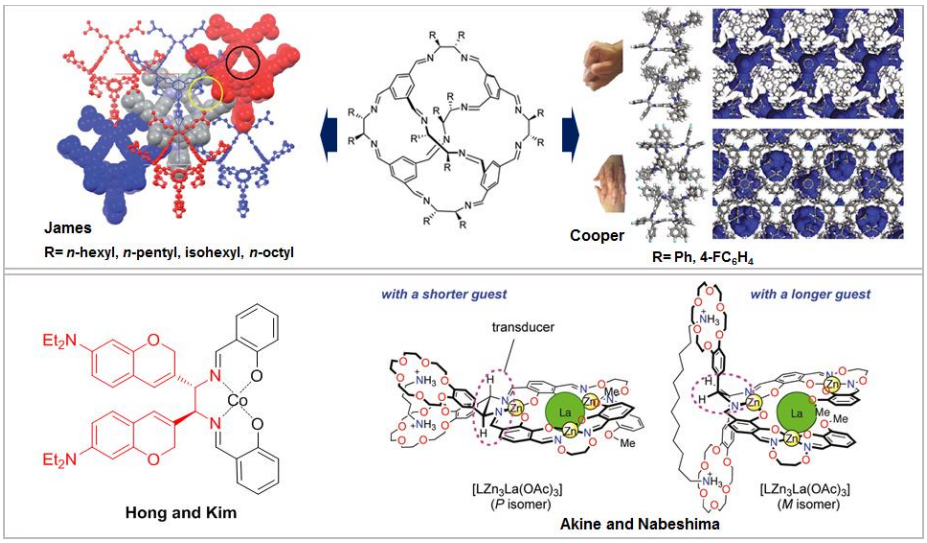


Figure 5. Other Applications of DCR.

anion developed by Hong and Kim were easily synthesized by DCR.[43] Also, Akine and Nabeshima[44] developed helical molecular levers with a novel crown ether chiral *dpen* derivative moiety starting from *hpen*. Cooper and James used the DCR to improve the properties of covalent or alkylated organic cages.[45]

Summary

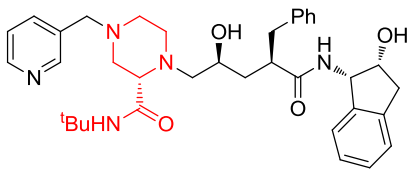
RAHB-directed DCR is a powerful method for the synthesis of a large number of chiral vicinal diamines as well as non-symmetrically substituted vicinal diamines since Vögtle introduced DCR for *meso* diamines. Also, it facilitates the structural tuning and electronic diversity of diamine functionality for the discovery and development of new transition metal based catalysts, organocatalysts and other applications. However, the diaza-Cope rearrangement has not found much use in the synthesis of chiral building blocks for biologically active compounds or peptidomimetic structures compared to the use for catalysts. This thesis is therefore focused on the development of novel synthetic methods for highly substituted chiral piperazines, chiral γ,δ-diamino ester and twinned alanine ester as key intermediates for the construction of therapeutically active agents. In addition, the use of ribose and arabinose as chiral derivatizing agents (CDAs) for the determination of the enantiopurities of various C_2-symmetric vicinal diamines including *dpen* is described.

Chapter I.

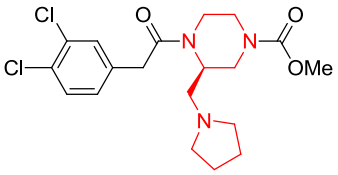
Synthesis of Chiral *trans*-3-Arylpiperazine-2-carboxylic Acid Derivatives

I-1. Introduction

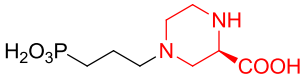
Piperazine is a versatile building block often employed in the design of physiologically active compounds.[1] Among various substituted piperazine structures, piperazine-2-carboxylic acid derivatives can be regarded as novel amino acid surrogates and therefore have been utilized in various peptidomimetic structures for therapeutically important molecules. Examples of chiral piperazine-2-carboxylic acid derivatives embedded in drug candidates include a human immunodeficiency virus (HIV) protease inhibitor,[2]



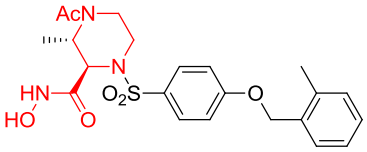
HIV protease inhibitor



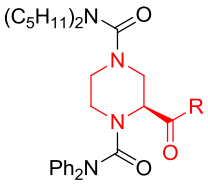
κ-receptor agonist



NMDA antagonist

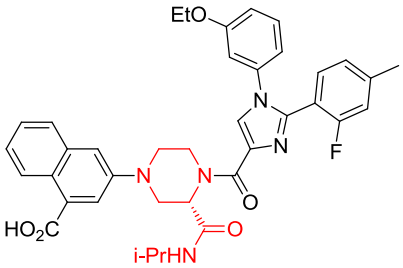


MMP-13 and TNF-α Converting Enzyme Inhibitor



R= -NH(CH$_2$)$_2$NHCH$_2$(2-OMe)Ph
R= -NH(CH$_2$)$_2$N(Me)CH$_2$(2-OMe)Ph

SP receptor antagonists



CCK1R agonist

Figure I-1. Compounds Containing Chiral Piperazine-2-carboxylic Acid Derivatives.

cholecystokinin-1 receptor (CCK1R) agonists,[3] κ-receptor agonists,[4] substance P (SP) receptor antagonists,[5] *N*-methyl-D-aspartic acid (NMDA) antagonists,[6] and MMP-13 and TNF-α converting enzyme inhibitors (Figure I-1).[7]

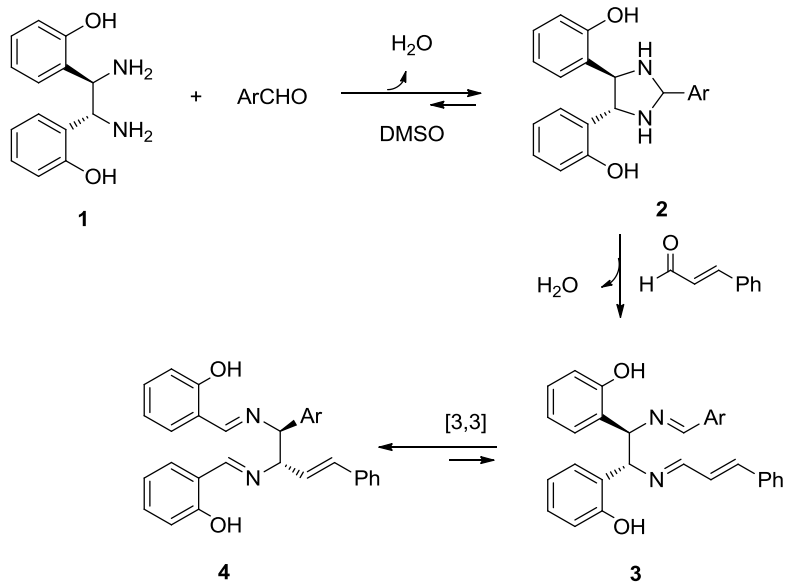
Although much research has been carried out for the synthesis of optically active piperazine-2-carboxylic acid derivatives, preparation of stereodefined 3-, 5- or 6-substituted piperazine-2-carboxylic acid derivatives in an enantiomerically pure form is still a challenging synthetic problem. Previously, chiral piperazine-2-carboxylic acid derivatives have been prepared through cyclizations,[8] multicomponent synthesis,[9] amino acid-based synthesis,[10] enzymatic resolution,[11] asymmetric hydrogenation of pyrazine derivatives,[12] α-lithiation of piperazine using *s*-BuLi/(-)-sparteine[13] and Pd-catalyzed asymmetric allylic allylation.[14] However, some of these methods suffer from shortcomings such as the problem of catalyst traces remaining in final product(s), low enantiopurity of final compounds and low yields resulting from complicated multistep route. In the course of our medicinal chemistry programs, we were in search of an efficient method for the preparation of *trans*-3-arylpiperazine-2-carboxylic acid derivatives and have found that there are scarce reports on them.[8g] To obtain 3-substituted piperazine-2-carboxylic acids, S_N2-type cyclization and the reduction of 2,3-disubstituted ketopiperazines derived from chiral 1,2-diamines have been previously used.[7,8g] For the latter method, synthesis of suitably substituted enantiopure chiral vicinal diamines is essential. We have recently developed a stereospecific synthesis of C_2-symmetric chiral vicinal diamines through the diaza-Cope rearrangement (DCR) of chiral initial diimines prepared from the reaction of (*R*,*R*)/(*S*,*S*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (*hpen*) and 2 equiv of aldehydes.[15] The rearrangement reaction was nicely extended to a stereospecific "one pot" route to α-substituted *syn*-α,β-diamino esters.[16] We envisioned that the chiral nonsymmetrical 1,2-disubstituted vicinal

diamines synthesized by diaza-Cope rearrangement (DCR) could serve as suitable intermediates for the preparation of chiral nonsymmetrical 2,3-substituted piperazines. Herein, we demonstrate on the development of an efficient route to enantiomerically pure *trans*-3-arylpiperazine-2-carboxylic acids starting from chiral *hpen* via DCR using various aryl aldehydes and *trans*-cinnamaldehyde.

I-2. Result and Discussion

Toward the construction of structurally diverse *trans*-3-arylpiperazine-2-carboxylic acids, formation of the unsymmetrically substituted diimines was studied from the reaction of *hpen* with benzaldehyde and *trans*-cinnamaldehyde. To find optimal reaction conditions, factors such as solvent, temperature and stoichiometry of aldehydes were investigated. From solvent screening experiments using dimethyl sulfoxide (DMSO), tetrahydrofuran (THF) and toluene, DMSO was quickly identified as the solvent of choice. As for the reaction stoichiometry, 1 equiv of aryl aldehyde and 1 equiv of *trans*-cinnamaldehyde were found to be optimal for the reaction. The reactions proceeded smoothly at ambient tem74perature, and reactions at higher temperatures did not improve the yield. Since two different aldehydes are involved in the reaction to form heterodimeric diimine product, the hetero- versus homodimer selectivity is critical. It was found that the best heterodimer selectivity was obtained when an aminal **2** was first formed and then was subjected to the reaction with *trans*-cinnamaldehyde, as outlined in Scheme I-1. The formation of the aminal **2** was accomplished through slow addition of an aryl aldehyde to the solution of *hpen*. The structure of aminal **2** was confirmed from ^{1}H NMR spectral analysis of a crude reaction mixture in

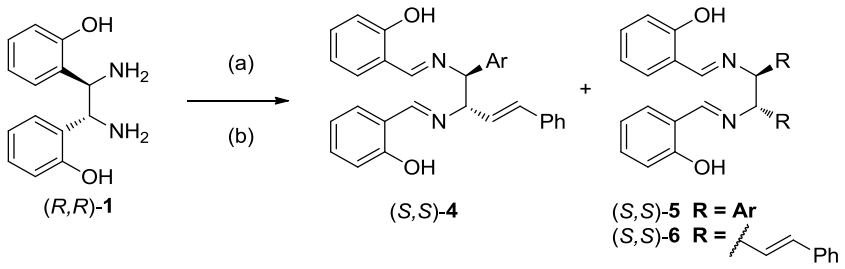
DMSO-d_6. This aminal **2** was then subjected to the reaction with *trans*-cinnamaldehyde without isolation. Addition of *trans*-cinnamaldehyde to aminal **2** then allowed for the formation of diimine 3, which was smoothly converted to the desired product diimine **4** facilitated by the RAHB.[17] The formation of diimine **4** as a major product was observed along with small amounts of homodimeric diimine products of each aldehyde.



Scheme I-1. Stereospecific Synthesis of Diimine via DCR.

With the optimized reaction conditions in hand, various aryl aldehydes were investigated in the formation of compound **2** to insure structural diversity of the chiral piperazine derivatives. Excellent yields (mostly >90%) of aminal intermediates **2** were observed as determined by NMR analysis.[18] In this step, slow addition of the aryl aldehyde was found to be critical to minimize the formation of homodimeric diimine product **5** or **6**. Subsequently, the formation of heterodimeric diimine **4** as a major product was confirmed 12 h after addition of 1 equiv *trans*-cinnamaldehyde.

Table I-1. Stereospecific Synthesis of Chiral Nonsymmetrical Disubstituted Diimines.[a]



Entry	Product	Ar	Yield (%)[b]	**4**/**5**/**6** ratio[b,c]
1	**4a**	Ph	89	88/7/5
2	**4b**	4-FC_6H_4	91	88/7/5
3	**4c**	4-ClC_6H_4	91	91/4/5
4	**4d**	2-BrC_6H_4	86	97/2/1
5	**4e**	3-BrC_6H_4	91	91/6/3
6	**4f**	4-BrC_6H_4	83	91/4/5
7	**4g**	1-Naphthyl	90	89/7/4
8	**4h**	2-Pyridyl	82	94/4/2
9	**4i**	4-$OMeC_6H_4$	71	79/13/8
10	**4j**	4-Acetamidophenyl	74	80/11/9

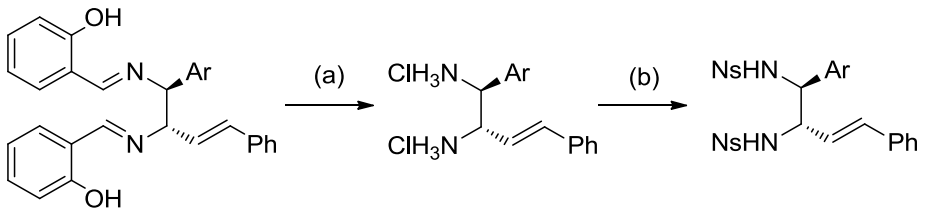
[a] Reagents and conditions: (a) ArCHO, DMSO, rt, 1 h; (b) *trans*-cinnamaldehyde, rt, 12 h.
[b] Determined by ^{1}H NMR analysis of the crude mixture.
[c] The relative R_f values of the homodimeric side products compared to the desired heterodimeric product vary depending upon their structures.

As can be seen in Table I-1, the yields of heterodimeric diimine **4** were dependent upon the substituents on aryl aldehydes. Diimines formed from an aryl aldehyde containing electron-withdrawing or halide substituents were obtained in good to excellent yields (entries **2**-**6**) with good hetero/homo

product ratios, which were determined through ^{1}H NMR analysis.[18] Diimines formed from 1-naphthyl and heteroaromatic aldehydes were also obtained in satisfactory yields (entries **7** and **8**). On the other hand, reactions of *p*-methoxybenzaldehyde and 4-acetamidobenzaldehyde gave moderate yields of product diimines and slightly higher ratios of unwanted homodimeric diimines (entries **9** and **10**, respectively).

Formation of the homodimeric product **6** of *trans*-cinnamaldehyde is believed to come from the very nature of the reaction, which involves the equilibrium from *hpen* and two aldehydes to the very end product, thus allowing for disproportionation after addition of *trans*-cinnamaldehyde. Attempts to purify the heterodimeric diimine products from the homodimeric diimines on a silica gel column were accompanied by some decomposition of the diimine species. Therefore, we decided to purify the heterodimeric product at a later stage.

Table I-2. Synthesis of *N*-Ns-Protected Vicinal Diamines[a]



(S,S)-**4** *(S,S)*-**7** *(S,S)*-**8**

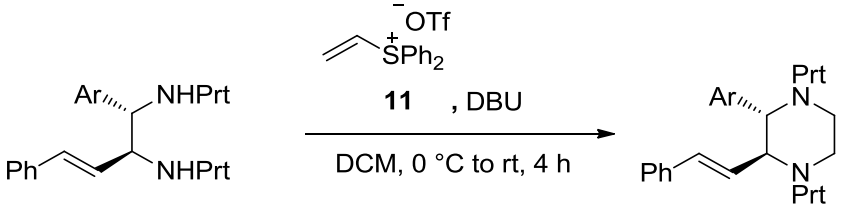
Entry	Product	Ar	Yield (%)[b]	Ee (%)[e]
1	**8a**	Ph	79	>99
2	**8b**	4-FC_6H_4	86	>99
3	**8c**	4-ClC_6H_4	84	>99
4	**8d**	2-BrC_6H_4	84	>99

5	**8e**	3-BrC_6H_4	83	>99
6	**8f**	4-BrC_6H_4	91	>99
7	**8g**	1-Naphthyl	76	>99
8	**8h**	2-Pyridyl	74[c,d]	>99
9	**8i**	4-OMeC_6H_4	76	>99
10	**8j**	4-Acetamidophenyl	59	>99[f]

[a] Reagents and conditions: (a) 2.5 equiv of conc. HCl in THF (0.1M); (b) 4 equiv of 4-NsCl, 6 equiv ofTEAinTHF(0.1 M).
[b] Yields of isolated products after column chromatography.
[c] Excess (3.5 equiv) conc. HCl was used.
[d] In this reaction, 8 equiv of TEA was used in dichloromethane.
[e] Values of ee were determined through chiral HPLC analysis using Chiralpak IA column.
[f] Value of ee was determined at the chiral diimine **4j** stage.

Hydrolysis of diimine **4** and subsequent protection of the resulting diamine **7** was carried out, and the data are shown in Table I-2. Upon hydrolysis of diimines **4a-j** using concentrated HCl, diamine HCl salts **7a-j** were obtained as precipitates. HCl salts **7a-j** underwent smooth reaction with 4-nitrobenzenesulfonyl chloride (NsCl) and triethylamine (TEA) in THF to give *N,N'*-bisNs-protected vicinal diamines **8a-j** in good overall yields (59-91% for the two steps). Enantiomeric purities of the product diamines were determined at this stage through chiral HPLC analysis, and all of them were uniformly high (>99% ee).

Table I-3. Annulation of Diamines with Various Protecting Groups[a]



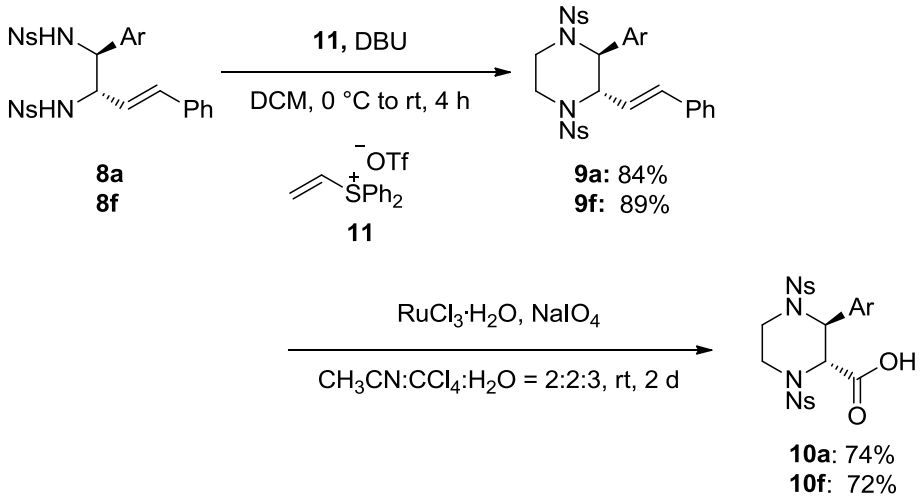
Entry	Prt	Base	Time	Yield (%)
1	-H	TEA	12 h	11[b]
2	-Bz	DBU	24 h	trace
3	-Boc	KOH	12 h	47[c]
4	-CF_3CO	DBU	12 h	66
5	-Ts	DBU	4 h	82
6	**-Ns**	**DBU**	**4 h**	**84**

[a] Reagents and conditions. 1.2 equiv diphenylvinylsulfonium triflate **11** and 2.2 equiv base were used in DCM (0.02 M).
[b] The product was purified after *N*-Boc protection.
[c] In this reaction, 6 equiv KOH and 6 equiv 18-crown-6 was used.

In 2008, Aggarwal *et al*. reported an annulation reaction for the synthesis of piperazines from ethylenediamine derivatives using diphenylvinylsulfonium triflate (**11**).[19] We took compound **7a** to study optimal reaction conditions for the construction of piperazine structures using Aggarwal's protocol. First, reactions using Aggarwal's diphenylvinylsulfonium triflate (**11**) were attempted on the free diamine of **7a**; however, the reaction was very sluggish, yielding only 11% of the desired piperazine product, which was confirmed after *N*-Boc protection. Diamines having various *N,N'*-protecting groups such as Boc, CBz, CF_3CO, Ts and Ns groups, which are associated with different pKa values,[20] were screened for the construction of piperazine ring (Table I-3). The reaction from *N,N'*-diBz-protected diamines gave almost no desired product at all. However, 47% yield of the desired piperazine ring was obtained in the reaction of the *N,N'*-bisBoc-protected diamine using potassium hydroxide as a base and 18-crown-6 as an additive to improve the solubility of KOH in the reaction. When more acidic *N,N'*-diNs or diTs groups, which allow lower pKa values on the nitrogen atoms compared to other protecting groups, were employed as protecting groups, the reactions

proceeded in good yields (82 and 84%, respectively). Even though both *N,N'*-diTs- and *N,N'*-diNs-protected diamines provided good yields of the desired product, *N,N'*-diNs protection, which can be deprotected via treatment with PhSH and K_2CO_3 in dimethylforamide (DMF),[21] was preferred since harsh reaction conditions would be required for the removal of the *N,N'*-diTs group. The *N,N'*-diNs protection provided another advantage where, at this stage, the heterodimeric amines were easily separable from the homodimeric diamine derivatives through silica gel column chromatography.

With the optimal protecting group selected, another substrate having a 4-bromophenyl substituent (**8f**) was tested for the ring forming reaction with diphenylvinylsulfonium triflate **11**, and the reaction proceeded in 89% yield, showing the generality of this cyclization. Eventually, the double bond moieties of **9a** and **9f** were efficiently oxidized into carboxylic acids via oxidation using ruthenium (III) chloride monohydrate with sodium periodate[22] in 74 and 72% yields, respectively (Scheme I-2).



Scheme I-2. Synthesis of Enantiopure *trans*-3-Arylpiperazine-2-carboxylic Acids.

I-3. Conclusion

A simple, yet highly efficient synthetic route for enantiopure *trans*-3-arylpiperazine-2-carboxylic acids as exemplified in **10a** and **10f** starting from *hpen* as a chiral starting material with various aryl aldehydes and *trans*-cinnamaldehyde has been developed. The chiral starting material, that is *hpen*, transfers its chirality to the product diimines, eventually leading to the formation of chiral piperazines in highly enantiopure form. Use of the chiral 3-arylpiperazine-2-carboxylic acids as an artificial amino acid analogue in the construction of physiologically active compounds is in progress and will be reported in due course.

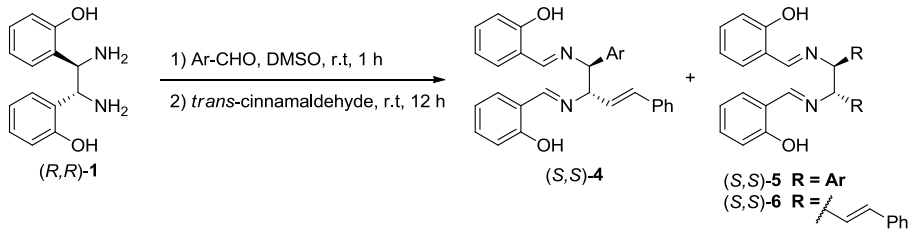
I-4. Experimental

General Information

The ^{1}H and ^{13}C NMR-spectra were measured with a Bruker DPX-300 (300 MHz) and a Varian/Oxford As-500 (500 MHz) spectrophotometer. ^{19}F NMR-spectra were measured with a Bruker, Avance-300 (300 MHz). Chemical shifts were measured as part per million (δ values) from tetramethylsilane as an internal standard at probe temperature in $CDCl_3$ or corresponding deuterated solvents for neutral compounds. High resolution mass spectra (HRMS) were recorded on a ThermoFinnigan LCQ™ Classic, Quadrupole Ion-Trap Mass Spectrometer. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC, UV detection monitored at 254.4 nm, using a Chiralpak® IA column (25 cm) or a Chiralcel OD-H column (25 cm). Optical rotation data were obtained on a JASCO P-1030 automatic polarimeter.

Melting points were recorded using an Electrothermal Melting Point Equipment IA 8103. Reactions that needed anhydrous conditions were carried out in flame-dried glassware under positive pressure of dry N_2 using standard Schrenk line techniques. Evaporation of solvents was performed at reduced pressure using a rotary evaporator. TLC was performed by silica gel 60 F_{254} coated on aluminum sheet (E. Merck, Art.5554). Chromatogram was visualized by UV-lamp (Vilber Lournat, VL-4LC). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60), and eluent was mentioned in each procedure. All materials were obtained from commercial supplier and used without further purification.

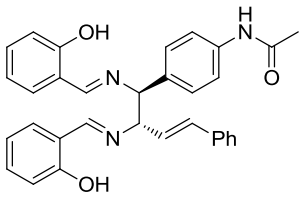
General procedure for synthesizing chiral nonsymmetrical disubstituted diimines



To a stirred solution of 100 mg (0.41 mmol) of (*R*,*R*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (*hpen*) in 1.2 mL of dimethylsulfoxide (DMSO) was slowly added 0.41 mmol of arylaldehyde in 0.2 mL of DMSO for 3 minutes using a syringe pump. The resulting solution was stirred for 1 h at room temperature. The formation of imidazolidine **2** was confirmed by taking ^{1}H NMR spectra of the reaction mixture in DMSO-d_6. 51.5 μL (0.41 mmol) of *trans*-cinnamaldehyde was added to the reaction mixture for minutes. ^{1}H NMR spectroscopy was used to monitor the progress of the

reaction and to determine the ratio between (*S*,*S*)-**4**, (*S*,*S*)-**5**, (*S*,*S*)-**6**. After stirring at room temperature for 12 h, the reaction mixture was mixed with iced-cold distilled water and extracted with diethyl ether. The combined organic layers were washed with distilled water twice and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained products were used for further reactions as obtained, without additional purification. (In the case of **4j**, diimine **4j** should be separated to determine enantiomeric excess of *N*-Nosyl diamine **8j** because we could not determine enantiomeric excess of **8j**.

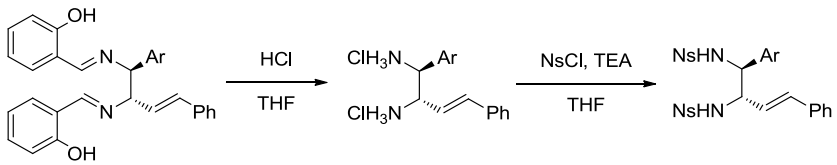
Compound (*S*,*S*)-**4j**



To a stirred solution of 100 mg (0.41 mmol) of (*R*,*R*)-*hpen* in 1.2 mL of DMSO was slowly added 0.41 mmol of 4-acetamidophenylbenzaldehyde in 0.2 mL of DMSO for 3 minutes using a syringe pump. The resulting solution was stirred for 1 h at room temperature. 51.5 μL (0.41 mmol) of *trans*-cinnamaldehyde was added to the reaction mixture for minutes. After stirring at room temperature for 12 h, the reaction mixture was mixed with iced-cold distilled water and extracted with diethyl ether. The combined organic layers were washed with distilled water twice and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was separated by column chromatography (Hexane/EtOAc) to afford **4j** as a solid. Yellow solid (52% yield), mp 228 ℃, R_f = 0.35 (Hexane:EtOAc = 1:1) ^{1}H NMR (499 MHz, $CDCl_3$): δ 13.32 (s, 1H), 13.25 (s, 1H), 8.34 (s, 1H), 8.30 (s, 1H), 7.71 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.25 – 7.14 (m, 9H), 6.93 (t, *J* = 9.2 Hz, 2H), 6.80 (dd, *J* = 12.0, 7.2 Hz, 2H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.16 (dd, *J* = 16.0, 6.7 Hz, 1H),

4.59 (d, J = 6.7 Hz, 1H), 4.39 (t, J = 6.6 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 166.5, 166.3, 161.20, 161.17, 138.0, 136.6, 135.5, 133.1, 132.9, 132.1, 128.8, 128.7, 128.1, 127.4, 126.7, 120.2, 119.09, 119.05, 118.9, 118.8, 117.21, 117.15, 78.2, 76.9, 24.8; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.3 ml/min); *rac*-**4j** t_R = 47.7 min t_R = 71.0 min. (*S*,*S*)-**4j** t_R = 47.4 min.; HRMS (ESI) calculated $C_{32}H_{30}O_3N_3$ $[M+H]^+$: 504.2282, Found: 504.2270; $[\alpha]_D^{28}$ -39.9 (c = 1.0, $CHCl_3$) for (*S*,*S*)-**4j**.

Preparation of *N*-Ns-Protected Vicinal Diamines

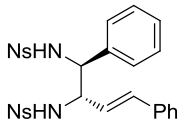


(*S*,*S*)-**4** (*S*,*S*)-**7** (*S*,*S*)-**8**

To a clear solution of obtained product (*S*,*S*)-**4** (*ca*. 0.41 mmol) in 4.1 mL (0.1 M) of THF was added 85.3 μL (1.03 mmol) of 12 M HCl solution. Stirring the reaction mixture at ambient temperature for 4 h afforded the product as a white precipitate. The solid was filtered and washed with THF to afford crude product as the dihydrochloride salt. In the case that the precipitate was not detected, 3 ml of distilled water pour into the reaction mixture and washed with diethyl ether three times. The aqueous layer was concentrated under reduced pressure to afford crude product as a solid. To a stirred solution of dihydrochloride salt in 4.1 mL of THF (0.1 M) was added 342.3 μL (2.46 mmol) of triethylamine (TEA) at ambient temperature. After 10 min, 272.6 mg (1.23 mmol) of 4-nitrobenzenesulfonyl chloride (4-NsCl) was added to the reaction mixture. After stirring at room temperature for 5 h,

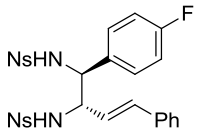
the reaction mixture was mixed with saturated $NaHCO_3$ and extracted with dichloromethane twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was separated by column chromatography (Hexane/EtOAc) to afford *N*-Ns protected products as a solid.

Compound (*S,S*)-**8a**



White solid (79% yield), mp 228 ℃, R_f = 0.25 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.78 (d, *J* = 9.6 Hz, 1H), 8.26 (d, *J* = 8.9 Hz, 1H), 8.14 – 8.08 (m, 2H), 8.08 – 8.01 (m, 2H), 7.89 – 7.82 (m, 2H), 7.77 – 7.70 (m, 2H), 7.14 – 6.95 (m, 8H), 6.82 (d, *J* = 7.2 Hz, 2H), 5.83 (d, *J* = 15.9 Hz, 1H), 5.46 (dd, *J* = 15.9, 8.1 Hz, 1H), 4.54 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.13 – 4.06 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 149.5, 149.4, 147.6, 147.4, 137.9, 136.1, 133.1, 128.9, 128.8, 128.53, 128.50, 128.45, 128.2, 127.8, 126.5, 125.5, 124.8, 124.5, 62.0, 61.3; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.3 ml/min); *rac*-**8a** t_R = 9.0 min t_R = 11.8 min. (*S,S*)-**8a** t_R = 11.8 min; HRMS (ESI) calculated for $C_{28}H_{23}O_8N_4S_2$ $[M-H]^-$: 607.0957 , Found: 607.0948; $[\alpha]_D^{23}$ -4.6 (c = 1.0, THF) for (*S,S*)-**8a**.

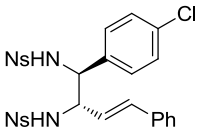
Compound (*S,S*)-**8b**



White solid (86% yield), mp 207 ℃, R_f = 0.23 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.75 (d, *J* = 9.7 Hz, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 8.08 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 8.9 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.19 – 7.05 (m, 5H), 6.90 – 6.77 (m, 4H), 5.89 (d, *J* = 15.9 Hz,

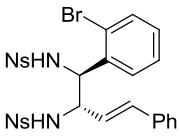
1H), 5.50 (dd, *J* = 15.9, 7.9 Hz, 1H), 4.57 (dd, *J* = 11.2, 5.1 Hz, 1H), 4.15 – 4.04 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.3, 160.1, 149.3, 147.3, 147.2, 147.01, 146.95, 135.8, 134.10, 134.06, 134.02, 132.9, 130.0, 129.9, 128.7, 128.6, 128.4, 128.3, 126.3, 125.32, 125.27, 124.6, 124.4, 115.2, 114.9, 61.1, 61.0, 60.9, 60.8; ^{19}F NMR (282 MHz, DMSO-d_6): δ -117.00; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.35 ml/min); *rac*-8b t_R = 14.2 min t_R = 17.6 min. (*S*,*S*)-**8b** t_R = 17.4 min.; HRMS (ESI) calculated for $C_{28}H_{22}O_8N_4FS_2$ [M-H]$^-$: 625.0863 , Found: 625.0853; $[\alpha]_D^{23}$ -6.4 (c = 1.0, THF) for (*S*,*S*)-**8b**.

Compound (*S*,*S*)-**8c**



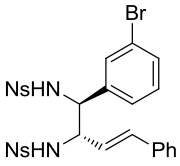
White solid (84% yield), mp 252 ℃, R_f = 0.25 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.70 (d, *J* = 9.7 Hz, 1H), 8.20 (d, *J* = 9.3 Hz, 1H), 8.13 (d, *J* = 8.9 Hz, 2H), 8.07 (d, *J* = 8.9 Hz, 2H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.75 (d, *J* = 8.9 Hz, 2H), 7.17 – 7.01 (m, 7H), 6.88 (d, *J* = 7.8 Hz, 2H), 5.94 (d, *J* = 15.9 Hz, 1H), 5.53 (dd, *J* = 15.9, 7.7 Hz, 1H), 4.58 (dd, *J* = 9.5, 6.6 Hz, 1H), 4.18 – 4.07 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 148.8, 146.7, 146.4, 136.4, 135.3, 132.4, 132.1, 129.3, 128.2, 128.0, 127.8, 127.8, 127.7, 125.9, 125.0, 124.1, 124.0, 60.4; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.35 ml/min); *rac*-**8c** t_R = 14.2 min t_R = 17.6 min. (*S*,*S*)-**8c** t_R = 17.4 min.; HRMS (ESI) calculated for $C_{28}H_{22}O_8N_4ClS_2$ [M-H]$^-$: 641.0568, Found: 641.0563; $[\alpha]_D^{23}$ +14.9 (c = 1.0, THF) for (*S*,*S*)-**8c**.

Compound (*S*,*S*)-**8d**



White solid (84% yield), mp 246 ℃, R_f = 0.18 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.98 (d, *J* = 9.2 Hz, 1H), 8.51 (d, *J* = 8.9 Hz, 1H), 8.08 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.09 – 7.04 (m, 3H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 7.7 Hz, 1H), 6.78 – 6.70 (m, 2H), 5.69 (d, *J* = 15.9 Hz, 1H), 5.45 (dd, *J* = 15.9, 8.7 Hz, 1H), 5.02 – 4.91 (m, 1H), 4.09 – 3.97 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.3, 149.2, 147.5, 146.7, 137.2, 135.6, 133.2, 132.4, 129.6, 129.4, 128.6, 128.3, 128.2, 128.1, 126.2, 124.6, 124.3, 123.6, 61.0, 59.9; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.35 ml/min); *rac*-**8d** t_R = 15.2 min t_R = 16.5 min. (*S*,*S*)-**8d** t_R = 16.5 min.; HRMS (ESI) calculated $C_{28}H_{22}O_8N_4BrS_2$ $[M-H]^-$: 685.0062 , Found: 685.0067; $[\alpha]_D^{23}$ -101.1 (c = 1.0, THF) for (*S*,*S*)-**8d**.

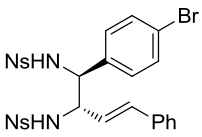
Compound (*S*,*S*)-**8e**



White solid (83% yield), mp 220 ℃, R_f = 0.25 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.68 (d, *J* = 9.8 Hz, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.9 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.18 – 7.08 (m, 6H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.91 – 6.83 (m, 2H), 5.94 (d, *J* = 15.9 Hz, 1H), 5.53 (dd, *J* = 15.9, 7.9 Hz, 1H), 4.55 (dd, *J* = 9.5, 6.7 Hz, 1H), 4.17 – 4.06 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 148.8, 146.7, 146.3, 139.8, 135.3, 132.5, 130.0, 128.2, 127.9, 127.8, 127.7, 126.9, 125.9, 124.9, 124.1, 123.9, 121.3, 60.6, 60.3; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100%

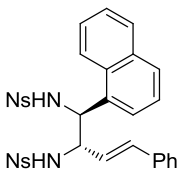
Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.3 ml/min); *rac*-**8e** t_R = 12.7 min t_R = 14.7 min. *(S,S)*-**8e** t_R = 14.5 min.; HRMS (ESI) calculated $C_{28}H_{22}O_8N_4BrS_2$ $[M-H]^-$: 685.0062 , Found: 685.0057; $[\alpha]_D^{23}$ -11.2 (c = 1.0, THF) for (*S,S*)-**8e**.

Compound (*S,S*)-**8f**



White solid (91% yield), mp 249 ℃, R_f = 0.25 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.69 (d, *J* = 9.7 Hz, 1H), 8.20 (d, *J* = 9.2 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.16 (dd, *J* = 22.3, 7.4 Hz, 5H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 7.6 Hz, 2H), 5.94 (d, *J* = 15.9 Hz, 1H), 5.53 (dd, *J* = 15.9, 7.7 Hz, 1H), 4.56 (dd, *J* = 9.4, 6.7 Hz, 1H), 4.17 – 4.07 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.3, 149.2, 147.2, 146.9, 137.3, 135.7, 132.9, 131.1, 130.1, 128.7, 128.5, 128.4, 128.3, 126.4, 125.5, 124.6, 124.5, 121.1, 61.0, 60.8; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine(DEA) 0.1%, 0.2 ml/min); *rac*-**8f** t_R = 25.2 min t_R = 30.0 min. (*S,S*)-**8f** t_R = 30.0 min.; HRMS (ESI) calculated $C_{28}H_{22}O_8N_4BrS_2$ $[M-H]^-$: 685.0062, Found: 685.0056: $[\alpha]_D^{23}$ +23.2 (c = 1.0, THF) for (*S,S*)-**8f**.

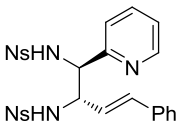
Compound (*S,S*)-**8g**



Yellow solid (76% yield), mp 229 ℃ , R_f = 0.23 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.93 (s, 1H), 8.35 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 7.9 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.69 (dd, *J* = 22.9, 8.1 Hz, 3H), 7.55 (dd, *J* = 12.9, 7.9 Hz, 4H), 7.42 (dd, *J* = 17.5, 7.6 Hz, 2H),

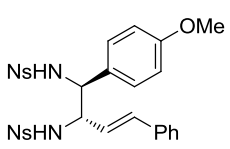
7.21 (t, *J* = 7.7 Hz, 1H), 7.05 (s, 3H), 6.70 (s, 2H), 5.91 (d, *J* = 15.5 Hz, 1H), 5.62 (s, 1H), 5.41 (s, 1H), 4.28 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 149.3, 149.2, 147.1, 146.9, 136.0, 134.4, 133.4, 130.9, 129.0, 128.8, 128.5, 128.4, 128.2, 127.1, 126.4, 126.2, 125.9, 125.7, 124.6, 124.1, 123.2, 60.9, 60.5; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1 %, 0.4 ml/min); *rac*-**8g** t_R = 12.1 min t_R = 15.6 min. (*S*,*S*)-**8g** t_R = 15.2 min.; HRMS (ESI) calculated $C_{32}H_{25}O_8N_4S_2$ $[M-H]^-$: 657.1114, Found: 657.1107; $[\alpha]_D^{23}$ -49.5 (c = 1.0, THF) for (*S*,*S*)-**8g**.

Compound (*S*,*S*)-**8h**



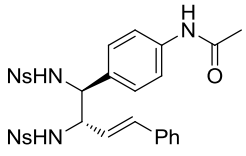
White solid (74% yield), mp 186 ℃, R_f = 0.08 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.67 (d, *J* = 9.7 Hz, 1H), 8.26 – 8.20 (m, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 4.8, 1.7 Hz, 3H), 7.01 (dd, *J* = 7.3, 4.9 Hz, 1H), 6.84 – 6.76 (m, 2H), 5.86 (d, *J* = 15.9 Hz, 1H), 5.55 (dd, *J* = 15.9, 7.8 Hz, 1H), 4.64 (dd, *J* = 9.6, 6.5 Hz, 1H), 4.35 – 4.28 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.9, 149.3, 149.2, 149.0, 147.4, 147.0, 136.8, 135.7, 132.5, 128.6, 128.5, 128.34, 128.25, 126.3, 125.9, 124.6, 124.4, 122.9, 122.6, 62.7, 60.3; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.3 ml/min); *rac*-**8h** t_R = 18.7 min t_R = 19.6 min. (*S*,*S*)-**8h** t_R = 19.5 min.; HRMS (ESI) calculated for $C_{27}H_{22}O_8N_5S_2$ $[M-H]^-$: 608.0904, Found: 608.0910; $[\alpha]_D^{23}$ -3.0 (c = 1.0, THF) for (*S*,*S*)-**8h**

Compound (*S*,*S*)-**8i**



Yellow solid (76% yield), mp 215 ℃, R_f = 0.18 (Hexane:EtOAc = 2:1), ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.63 (d, *J* = 9.7 Hz, 1H), 8.21 (d, *J* = 9.1 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.16 – 7.08 (m, 3H), 6.92 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 7.3 Hz, 2H), 6.50 (d, *J* = 8.2 Hz, 2H), 5.89 (d, *J* = 15.9 Hz, 1H), 5.51 (dd, *J* = 15.9, 7.8 Hz, 1H), 4.49 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.15 – 4.03 (m, 1H), 3.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.8, 149.2, 147.4, 147.2, 135.9, 132.7, 129.6, 129.2, 128.7, 128.5, 128.3, 128.2, 126.3, 125.7, 124.6, 124.3, 113.6, 61.2, 61.1, 55.3; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, 100 % Ethyl alcohol + diethyl amine (DEA) 0.1 %, 0.3 ml/min); *rac*-**8i** t_R = 15.1 min t_R = 21.3 min. (*S*,*S*)-**8i** t_R = 21.1 min.; HRMS (ESI) calculated $C_{29}H_{25}O_9N_4S_2$ [M-H]$^-$: 637.1063, Found: 637.1055; $[\alpha]_D^{23}$ +4.6 (c = 1.0, THF) for (*S*,*S*)-**8i**.

Compound (*S*,*S*)-**8j**

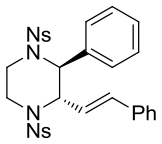


White solid (59% yield), mp 281 ℃, R_f = 0.30 (Hexane:EtOAc = 1:2), ^{1}H NMR (499 MHz, DMSO-d_6): δ 9.70 (s, 1H), 8.59 (d, *J* = 9.7 Hz, 1H), 8.19 (d, *J* = 9.1 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 2H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 5H), 6.90 (dd, *J* = 13.8, 7.8 Hz, 4H), 5.93 (d, *J* = 15.9 Hz, 1H), 5.54 (dd, *J* = 15.8, 7.7 Hz, 1H), 4.50 (dd, *J* = 9.3, 7.1 Hz, 1H), 4.16 – 4.06 (m, 1H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5, 149.2, 147.4, 147.1, 138.9, 135.9, 132.6, 132.1, 128.7, 128.4, 128.3, 128.2, 128.1, 126.3, 126.0, 124.5, 124.3, 118.4, 61.2, 61.1, 24.3: HRMS (ESI) calculated $C_{30}H_{26}O_9N_5S_2$ [M-H]$^-$:

664.1172, Found: 664.1161: $[\alpha]_D^{23}$ +22.0 (c = 1.0, THF) for (*S*,*S*)-**8j**.

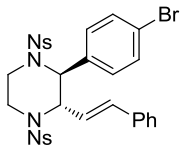
Synthesis of Piperazines from *N*-Nosyl Vicinal Diamines

Compound (*S*,*S*)-**9a**



N-Nosyl diamine **8a** (856 mg, 1.41 mmol) was dissolved into anhydrous CH_2Cl_2 (70.3 mL), stirred at 0 ℃ under nitrogen and treated with DBU (462.6 μL, 3.09 mmol). After 10 min, a solution of diphenylvinylsulfonium salt **11** (611 mg, 1.68 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise over two min. The reaction mixture was further stirred for 4 h and allowed to warm to room temperature. The reaction mixture was quenched with sat. ammonium chloride solution and extracted with CH_2Cl_2 twice, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was then purified using column chromatography on silica (Hexane:EtOAc = 4:1). The desired product **9a** was obtained as a white solid (750 mg, 84% yield); R_f = 0.33 (Hexane:EtOAc = 2:1); mp 306 ℃; ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.06 (t, *J* = 9.0 Hz, 4H), 7.98 (d, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.16 (s, 3H), 6.89 (d, *J* = 4.5 Hz, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 5.69 (dd, *J* = 16.0, 6.1 Hz, 1H), 5.17 (s, 1H), 5.09 (d, *J* = 5.9 Hz, 1H), 3.97 (d, *J* = 13.4 Hz, 1H), 3.69 (d, *J* = 12.5 Hz, 1H), 3.49 (t, *J* = 10.4 Hz, 1H), 3.39 (t, *J* = 9.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.8, 149.6, 145.1, 144.2, 137.6, 135.5, 133.5, 129.0, 128.9, 128.62, 128.59, 127.9, 127.3, 126.5, 125.0, 124.8, 124.6, 61.2, 59.3, 41.4; HRMS (ESI) calculated $C_{30}H_{25}O_8N_4S_2$ $[M-H]^-$: 633.1114, Found: 633.1106. $[\alpha]_D^{23}$ -14.12 (c = 1.0, THF) for (*S*,*S*)-**9a**.

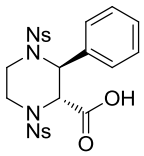
Compound (*S*,*S*)-**9f**



N-Nosyl diamine **8f** (857 mg, 1.25 mmol) was dissolved into anhydrous CH_2Cl_2 (62.3 mL), stirred at 0 ℃ under nitrogen and treated with DBU (410.1 μL, 2.74 mmol). After 10 min, a solution of diphenylvinylsulfonium salt **11** (542 mg, 1.50 mmol) in CH_2Cl_2 (4.5 mL) was added dropwise over two min. The reaction mixture was further stirred for 4 h and allowed to warm to room temperature. The reaction mixture was quenched with sat. ammonium chloride solution and extracted with CH_2Cl_2 twice, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was then purified using column chromatography on silica (Hexane:EtOAc = 4:1). The desired product **9f** was obtained as a white solid (790 mg, 89% yield); R_f = 0.30 (Hexane:EtOAc = 2:1); mp 274 ℃; ^{1}H NMR (499 MHz, DMSO-d_6): δ 8.12 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.19 – 7.13 (m, 3H), 6.90 (dd, *J* = 6.5, 2.8 Hz, 2H), 6.41 (d, *J* = 15.8 Hz, 1H), 5.71 (dd, *J* = 16.0, 5.7 Hz, 1H), 5.16 (s, 1H), 5.01 (d, *J* = 5.7 Hz, 1H), 3.93 (dt, *J* = 12.7, 3.9 Hz, 1H), 3.70 (dt, *J* = 8.4, 3.9 Hz, 1H), 3.62 – 3.52 (m, 1H), 3.51 – 3.44 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.2, 149.1, 144.1, 143.7, 136.70, 135.0, 132.8, 131.2, 128.9, 128.4, 128.13, 128.07, 126.0, 124.8, 124.5, 124.3, 120.9, 60.3, 59.1, 41.1, 40.5; HRMS (ESI) calculated $C_{30}H_{24}O_8N_4BrS_2$ $[M-H]^-$: 711.0219, Found: 711.0204; $[\alpha]_D^{23}$ -0.76 (c = 1.0, THF) for (*S*,*S*)-**9f**.

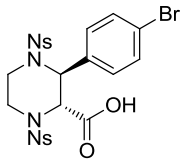
Synthesis of Enantiopure *trans*-3-Arylpiperazine-2-carboxylic Acids

Compound (*R*,*S*)-**10a**



N-Nosyl piperazine **9a** (73.1 mg, 0.115 mmol), CH_3CN (1.2 mL), CCl_4 (1.2 mL), H_2O (1.8 mL) and $NaIO_4$ (197.1 mg, 0.922 mmol) was stirred to a uniform suspension. $RuCl_3 \cdot H_2O$ (0.72 mg, 0.00346 mmol) was added, and the reaction was stirred for 2 days at ambient temperature. The reaction was quenched with 2 M HCl (8 mL) and then extracted with EtOAc three times. The organic layers were filtered through a Celite, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then purified using column chromatography on silica (Hexane:EtOAc:AcOH = 3:1:0.01). The desired product **10a** was obtained as a white solid (49 mg, 74% yield); R_f = 0.33 (Hexane:EtOAc:AcOH = 3:1:0.01); mp 208 ℃; ^{1}H NMR (499 MHz, Acetone-d_6): δ 8.30 (d, J = 8.5 Hz, 2H), 8.24 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.41 – 7.29 (m, 3H), 5.85 (s, 1H), 5.23 (s, 1H), 3.99 (d, J = 10.9 Hz, 1H), 3.85 (d, J = 9.6 Hz, 1H), 3.50 – 3.36 (m, 2H); ^{13}C NMR (75 MHz, Acetone-d_6): δ 169.1, 150.11, 150.05, 145.7, 145.0, 136.3, 128.8, 128.6, 128.5, 128.0, 127.2, 124.4, 124.2, 58.9, 57.8, 41.4, 40.7; HRMS (ESI) calculated $C_{23}H_{19}O_{10}N_4S_2$ $[M-H]^-$: 575.0543, Found: 575.0537; $[\alpha]_D^{23}$ +3.65 (c = 1.0, THF) for (*R*,*S*)-**10a**.

Compound (*R*,*S*)-**10f**



N-Nosyl piperazine **9f** (125 mg, 0.175 mmol), CH_3CN (2.0 mL), CCl_4 (2.0 mL), H_2O (3.0 mL) and $NaIO_4$ (300 mg, 1.4 mmol) was stirred to a uniform suspension. $RuCl_3 \cdot H_2O$ (1.1 mg, 0.0053 mmol) was added, and the reaction was stirred for 2 days at ambient temperature. The reaction was quenched with 2 M HCl (14 mL) and then the reaction mixture was extracted with EtOAc (15 mL) three times from aqueous phase. The organic layers were filtered through a Celite, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was then purified using column chromatography on silica (Hexane:EtOAc:AcOH = 3:1:0.01). The desired product **10f** was obtained as a white solid (82.1 mg, 72% yield); R_f = 0.33 (Hexane:EtOAc:AcOH = 3:1:0.01); mp 258 ℃; ^{1}H NMR (499 MHz, Acetone-d_6): δ 8.30 – 8.19 (m, 4H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 5.88 (s, 1H), 5.18 (s, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 3.84 (d, *J* = 11.7 Hz, 1H), 3.50 – 3.31 (m, 2H); ^{13}C NMR (126 MHz, Acetone-d_6): δ 169.4, 150.3, 150.2, 145.7, 145.3, 136.4, 132.0, 129.6, 129.0, 128.8, 124.7, 124.2, 121.8, 59.3, 57.7, 41.6, 40.9; HRMS (ESI) calculated $C_{23}H_{18}O_{10}N_4BrS_2$ $[M-H]^-$: 652.9648, Found: 652.9644; $[\alpha]_D^{23}$ +8.6 (c = 1.0, THF) for (*R*,*S*)-**10f**.

Chapter II.

Stereospecific Synthesis of γ,δ-Diamino Esters

II-1. Introduction

γ,δ-Diamino acid functionality is a core structure often embedded in physiologically active molecules (Figure II-1). This moiety has been found as useful intermediates for the preparation of therapeutic agents such as selective nonpeptide substance P receptor antagonists (CP-96,345 and CP-99,994),[1] dipeptidyl peptidase IV (DDP4) inhibitor (SYR-322),[2] potent factor Xa inhibitor,[3] potent nootropic drug (Unifiram, DM 232)[4] and antiviral agents (Oseltamivir (**1**), Zanamivir (**2**)).[5] In particular, with a possible avian flu[6] or swine flu[7] pandemic, the synthetic challenge of oseltamivir[8] together have recently attracted considerable interest in developing efficient methods for making the antiviral agent.[9] Elegant methods for making analogs of the antiviral agent would be useful for combating drug resistance.[10]

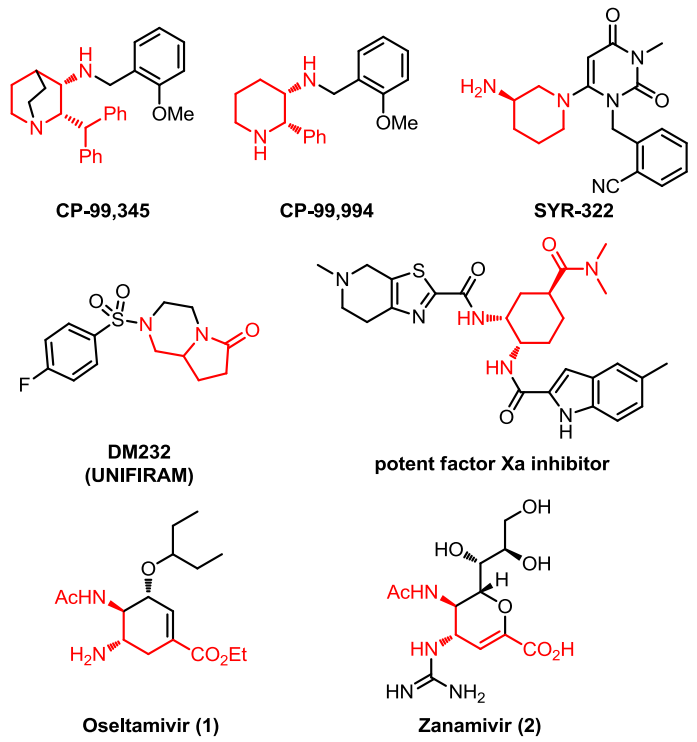
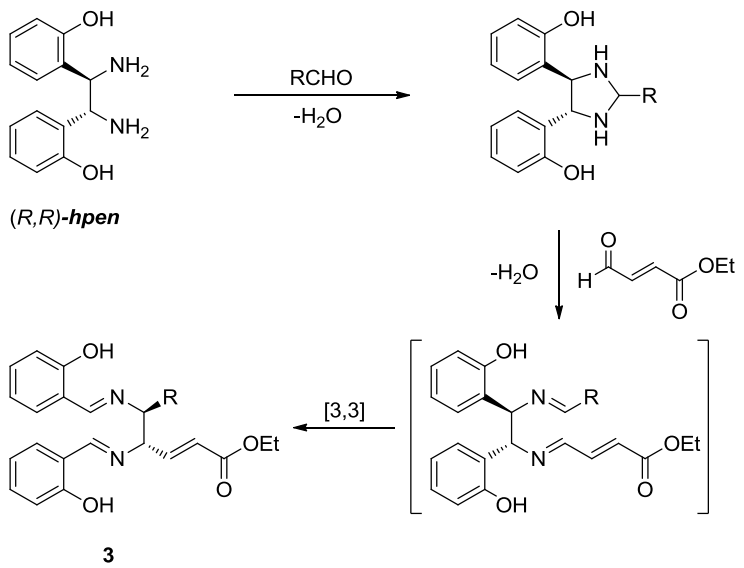


Figure II-1. Compounds Containing γ,δ-Diamino Acid Core

We have previously shown that diaza-Cope rearrangement (DCR) can be used to prepare a wide variety of aryl and alkyl substituted chiral vicinal diamines as well as non-symmetrically substituted chiral vicinal diamines.[11] Here we report stereospecific synthesis of γ,δ-diamino esters by using the rearrangement reaction..

II-2. Result and Discussion

For the synthesis of **3a** to **3d**, 1 equiv of the corresponding aryl aldehyde is allowed to react with (*R,R*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (*hpen*, 0.15 mmol) in DMSO (0.3 M, 0.5 mL) at ambient temperature for 1 h to form the imidazolidine intermediate, which was confirmed from ^{1}H NMR spectra of the reaction mixture in DMSO-d_6 (Scheme II-1). Ethyl *trans*-4-oxo-2-butenoate (0.17 mmol) is then added to the reaction mixture and stirred at ambient temperature for 2 h for the diaza-Cope rearrangement (DCR).[11]



Scheme II-1. Stereospecific Synthesis of γ,δ-Diimino Ester Derivatives.

In case of the alkyl substituted diimines (**3e** to **3g**), toluene was used instead of DMSO as a solvent. The diaza-Cope rearrangement required 1 h of heating at 110 ℃. The crude products (**3a** to **3g**) were purified by flash chromatography.

Figure II-2 shows the crystal structure of the product diimine (**3d**) formed from the reaction of (*R,R*)-*hpen* and 2,6-dichlorobenzaldehyde. The diaza-Cope rearrangement reaction gives the product diimine in *S,S* configuration as expected from the chair-like six-membered ring transition state with all equatorial substituents.

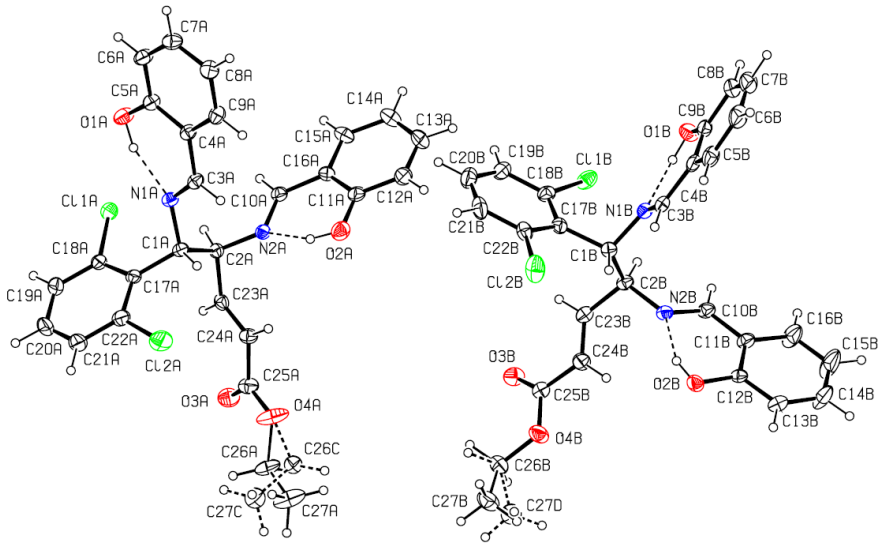
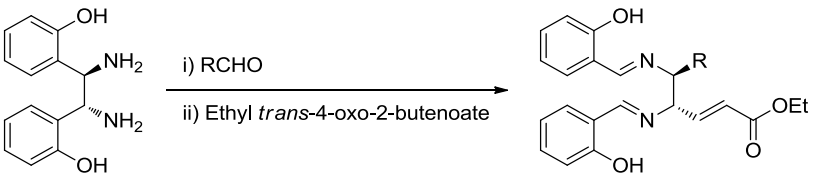


Figure II-2. Crystal Structure of Diimine **3d**.

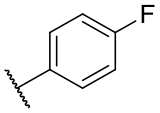
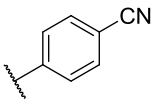
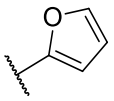
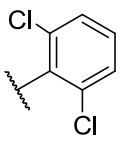
Table II-1 shows that the rearrangement reaction takes place with good yield and excellent stereospecificity for diimines containing aryl substituent (entries **1**-**4**). Most aryl aldehydes smoothly formed the imidazolidine intermediates. The aldehyde containing *ortho*-substituents (**3d**) takes about 2 h to form the imidazolidine intermediate due to steric hindrance. In case of diimines containing alkyl substituent, the rearrangement reaction gives the product

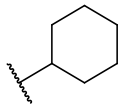
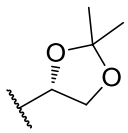
diimines in moderate yield and excellent stereospecificity (entries **5** to **7**). Thus a wide variety of alkyl and aryl substituted γ,δ-diamino ester derivatives can be synthesized stereosepecifically in a one-pot reaction by using the diaza-Cope rearrangement.

Table II-1. Synthesis of γ,δ-Diamino Ester Derivatives[a]



(*R,R*)-***hpen*** (*S,S*)-**3**

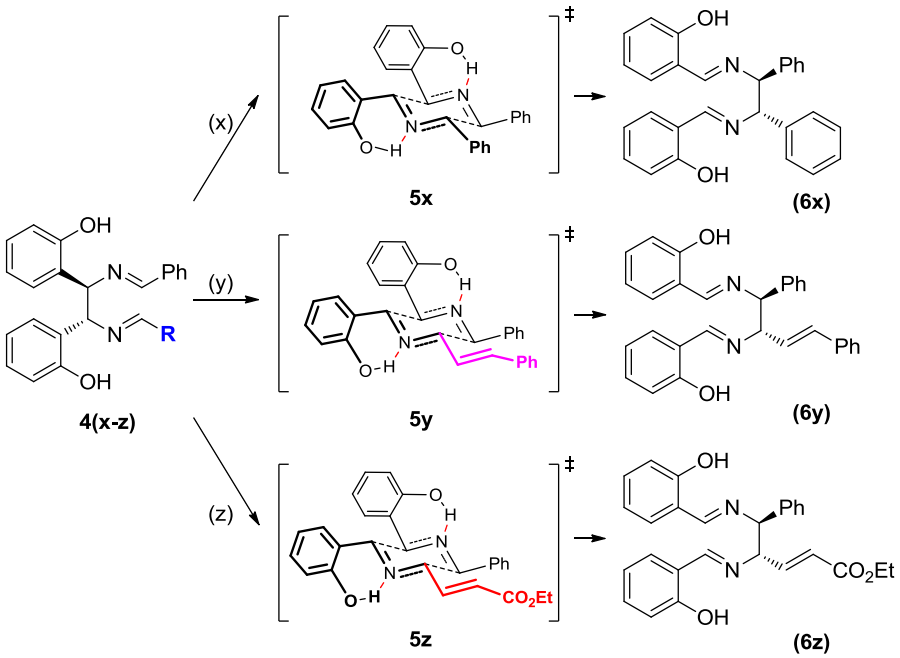
Entry	R	Solvent	Temp.[b]	Yield(%)[c]	Ee(%)[d]
1	 **3a**	DMSO	RT(1)/RT(2)	74	>99
2	 **3b**	DMSO	RT(1)/RT(2)	80	>99
3	 **3c**	DMSO	RT(1)/RT(2)	79	>99
4	 **3d**	DMSO	RT(2)/RT(2)	78	>99

5	 **3e**	Toluene	RT(1)/110(1)	62	>99
6	 **3f**	Toluene	RT(1)/110(1)	53	>99
7[e]	 **3g**	Toluene[f]	RT(2)/110(1)	50	>99

[a] Reaction conditions. i) (*R,R*)-*hpen* (0.15 mmol), aldehyde (0.15 mmol), solvent (0.3 M) ii) Ethyl *trans*-4-oxo-2-butenoate (0.17 mmol).
[b] Reaction time is in round bracket.
[c] Yield of isolated products.
[d] Ee was determined by chiral HPLC analysis using Chiralpak® IA column.
[e] The absolute configuration of obtained product is (*S,R*)-form.
[f] Toluene (0.1 M) was used for the reaction.

Aryl[12] and alkyl[13] aldehydes as well as *trans*-cinnamaldehyde [14] can be used to make diamines via the diaza-Cope rearrangement. The aldehyde conjugated to ester is more reactive than benzaldehyde or *trans*-cinnamaldehyde for the rearrangement reaction. DFT computation (B3LYP at 6-31G* level) shows that the energy barrier for the rearrangement is the lowest for **4z** (Scheme II-2), which bodes well with the experimental observation. Electron deficient aldehydes are generally more reactive than electron rich ones towards the DCR.[11f] In addition, the aldehyde conjugated to ester that is used to make **4z** is not only less sterically hindered because of the different size between phenyl group in benzaldehyde and olefin group, but also more reactive because of electronic difference between the ester and phenyl groups in *trans*-cinnamaldehyde for the rearrangement reaction.

Alkyl aldehydes are found to be less reactive than aryl aldehydes for diaza-Cope rearrangement. Chin's group previously showed that there is an energy difference of 5.4 kcal/mol between the transition states of diphenyl-substituted diimine and diisopropyl-substituted one.[13] Thus, it required harsher conditions to prepare dialkyl substituted products while the preparation of diaryl substituted product diimines were readily achieved at room temperature.

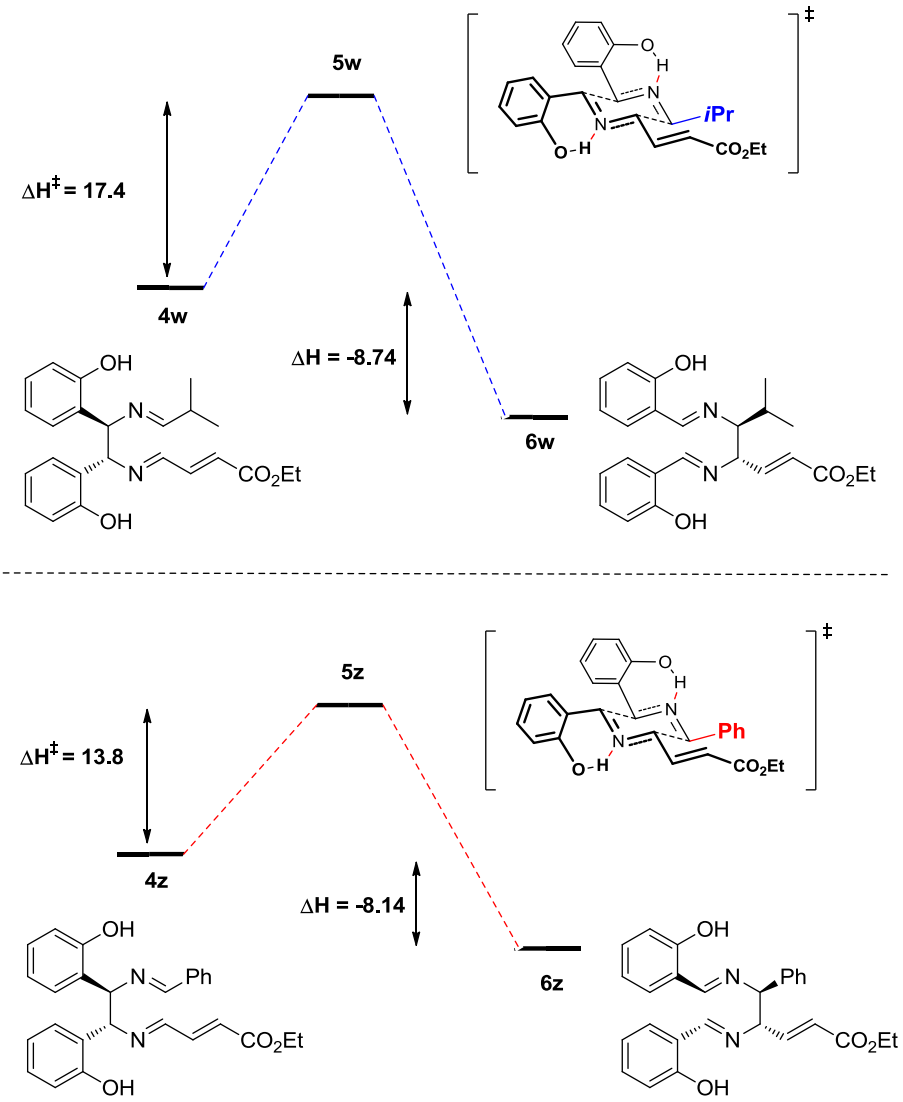


R		$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta H^{\ddagger} - \Delta H_z^{\ddagger}$
Ph	(x)	15.9	2.1
Ph	(y)	14.9	1.1
CO_2Et	(z)	13.8	-

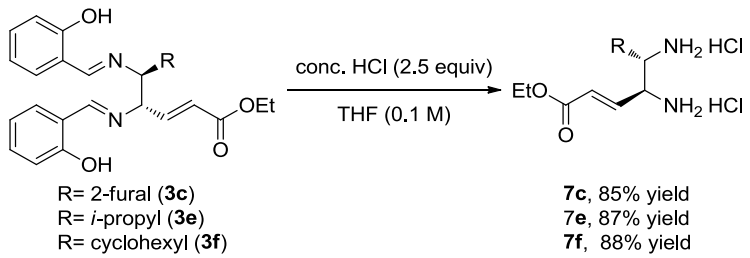
Scheme II-2. Calculated Activation Enthalpies for the DCR.[15]

In the same context, the synthesis of **3e-3g** required higher temperature than that of **3a-3d,** even though the half of substituents on diimine was derived

from ethyl *trans*-4-oxo-2-butenoate. Moreover, we realized the use of ethyl *trans*-4-oxo-2-butenoate led to shorter reaction time compared to previous work.[13] Also DFT computation shows that the energy barriers for formation of **3a-3d** are lower than those for formation of **3e-3g**, which is in good agreement with the experimental data (Scheme II-3).



Scheme II-3. Energy profile for the DCR Process of Aryl and Alkyl Diimines Substituted with Conjugated Ester (Energy values in kcal/mol).[15]



Scheme II-4. Hydrolysis of Diimines.

Hydrolysis of diimines **3c**, **3e**, and **3f** was carried out with concentrated HCl in THF as previously reported.[12] The reaction gave the corresponding chiral γ,δ-diamino ester dihydrochlorides as precipitates in 85%, 87% and 88% yields respectively (Scheme II-4).

II-3. Conclusion

In summary, we have shown that ethyl *trans*-4-oxo-2-butenoate can be used for the preparation of a variety of γ,δ-diimino esters by the diaza-Cope rearrangement followed by hydrolysis of the diimines. Both DFT computation and experimental results show that this conjugated aldehyde is more reactive than other aromatic or aliphatic aldehydes for the rearrangement reaction. In addition, it was found that the diimines with aryl substituents rearrange more readily than diimines with alkyl substituents.

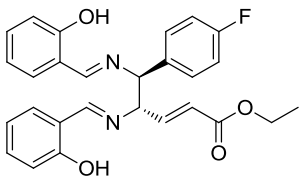
II-4. Experimental

General Information.

Commercially available compounds were used without further purification or drying. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer or a Bruker Advance III spectrometer operating at 400 MHz. High resolution mass spectra (HRMS) were obtained on an ABI/Sciex QStar Mass Spectrometer (ESI) at Advanced Instrumentation for Molecular Structure (AIMS) at the University of Toronto and on a ThermoFinnigan LCQ™ Classic, Quadrupole Ion-Trap Mass Spectrometer at Seoul National University. Optical rotation was obtained at 589 nm using a Rudolph Autopol IV polarimeter at the University of Toronto and on a JASCO P-1030 automatic polarimeter at Seoul National University. Melting points were recorded using an Electrothermal IA 9100 digital melting point apparatus. Reactions were monitored using ^{1}H NMR spectroscopy. Chromatography was performed on Silicycle 230-400 mesh silica gel and thin-layer chromatography (TLC) was performed on EMD Silica Gel 60 F_{254} plates. Visualization of the developed plates was performed under UV light (254 nm). HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC, UV detection monitored at 254.4 nm using a Chiralpak® IA column (25cm) at Seoul national university.

Preparation of γ,δ-diimino ester derivatives.

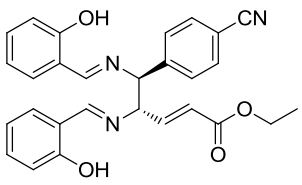
Compound (*S,S*)-**3a**



To a stirred solution of 36.6 mg (0.15 mmol) of (*R,R*)-*hpen* in 0.5 mL of DMSO (0.3 M) was added 4-fluorobenzaldehyde (0.15 mmol). The resulting solution was stirred for 1 h at room temperature. The formation of imidazolidine was confirmed by taking ^{1}H NMR spectra of the reaction mixture in DMSO-d_6. 20 µL of ethyl *trans*-4-oxo-2-butenoate (0.17 mmol) was added to the reaction mixture in one portion. After stirring at room temperature for 2 h, the reaction mixture was mixed with distilled water (30 mL) and extracted with diethyl ether. The combined organic layers were washed with brine/water (1:1) three times and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with ethyl acetate / *n*-hexanes (15 %) gave the desired product. Yellow solid (74 % yield); mp 82-83 ^{o}C, R_f = 0.25 (*n*-Hexane:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.91 (s, 1H), 12.75 (s, 1H), 8.34 (s, 1H), 8.25 (s, 1H), 7.40 – 7.27 (m, 4H), 7.21 – 7.14 (m, 2H), 7.07 (t, *J* = 8.7 Hz, 2H), 6.98 – 6.79 (m, 6H), 5.86 (dd, *J* = 15.7, 1.5 Hz, 1H), 4.57 (d, *J* = 7.3 Hz, 1H), 4.38 – 4.30 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H) 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.60, 166.75, 165.77, 161.01, 160.96, 144.33, 134.84, 134.80, 133.22, 133.07, 132.13, 132.07, 129.57, 129.49, 123.96, 119.12, 119.09, 118.50, 118.44, 117.21, 117.10, 116.18, 115.96, 77.21, 75.99, 60.77, 14.29; ^{19}F NMR (377 MHz, $CDCl_3$): δ -113.44; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, *n*-Hexane : EtOH = 7:3, 1.0 ml/min), *Rac*-**3a** t_R= 13.412 min, t_R = 35.636 min, (*S,S*)-**3a** t_R= 13.316 min; $[\alpha]_D^{27}$ +52.5 (c =

1.0, $CHCl_3$); HRMS (ESI) calculated for $C_{27}H_{26}FN_2O_4$ $[M+H]^+$: 461.1877, Found:.461.1859.

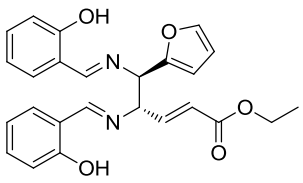
Compound (*S*,*S*)-**3b**



To a stirred solution of 36.6 mg (0.15 mmol) of (*R*,*R*)-*hpen* in 0.5 mL of DMSO (0.3 M) was added 4-cyanobenzaldehyde (0.15 mmol). The resulting solution was stirred for 1 h at room temperature. The formation of imidazolidine was confirmed by taking ^{1}H NMR spectra of the reaction mixture in DMSO-d_6. 20 µL of ethyl *trans*-4-oxo-2-butenoate (0.17 mmol) was added to the reaction mixture in one portion. After stirring at room temperature for 2 h, the reaction mixture was mixed with distilled water (30 mL) and extracted with diethyl ether. The combined organic layers were washed with brine/water (1:1) three times and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with ethyl acetate / *n*-hexanes (20 %) gave the desired product. Yellow solid (80 % yield), mp 100-101 ^{o}C, R_f = 0.33 (*n*-Hexane:EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.69 (s, 1H), 12.60 (s, 1H), 8.37 (s, 1H), 8.25 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.27 (m, 2H), 7.21 – 7.14 (m, 2H), 6.99 – 6.93 (m, 2H), 6.91 – 6.81 (m, 3H), 5.85 (dd, *J* = 15.7, 1.5 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 4.40 – 4.31 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.94, 167.59, 165.56, 160.98, 160.94, 144.18, 143.53, 133.47, 133.46, 132.83, 132.25, 132.21, 128.76, 124.53, 119.28, 119.24, 118.49, 118.32, 118.31, 117.28, 117.21, 112.45, 77.61, 75.65, 60.91, 14.28; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, *n*-Hexane:EtOH = 7:3, 1.0 ml/min), *Rac*-**3b** t_R= 33.564 min, t_R = 51.251 min, (*S*,*S*)-**3b** t_R= 33.173 min; $[\alpha]_D^{27}$

+3.55 (c = 1.0, $CHCl_3$); HRMS (ESI) calculated for $C_{28}H_{26}N_3O_4$ $[M+H]^+$: 468.1923, Found: 468.1917.

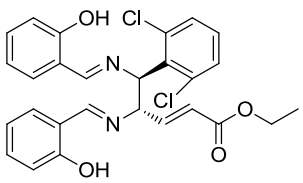
Compound (*S*,*S*)-**3c**



To a stirred solution of 36.6 mg (0.15 mmol) of (*R*,*R*)-*hpen* in 0.5 mL of DMSO (0.3 M) was added 2-furaldehyde (0.15 mmol). The resulting solution was stirred for 1 h at room temperature. The formation of imidazolidine was confirmed by taking ^{1}H NMR spectra of the reaction mixture in DMSO-d_6. 20 µL of ethyl *trans*-4-oxo-2-butenoate (0.17 mmol) was added to the reaction mixture in one portion. After stirring at room temperature for 2 h, the reaction mixture was mixed with distilled water (30 mL) and extracted with diethyl ether. The combined organic layers were washed with brine/water (1:1) three times and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with ethyl acetate / *n*-hexanes (15 %) gave the desired product. Yellow oil (79% yield), R_f = 0.31 (*n*-Hexane:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.79 (s, 1H), 12.74 (s, 1H), 8.31 (s, 1H), 8.30 (s, 1H), 7.44 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.34 – 7.25 (m, 2H), 7.23 – 7.16 (m,z 2H), 7.02 – 6.90 (m, 3H), 6.88 – 6.80 (m, 2H), 6.39 – 6.29 (m, 2H), 5.94 (dd, *J* = 15.7, 1.5 Hz, 1H), 4.76 (d, *J* = 7.4 Hz, 1H), 4.62 – 4.51 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.73, 167.27, 165.88, 161.05, 161.04, 151.20, 144.25, 142.95, 133.17, 133.07, 132.14, 132.13, 123.92, 119.06, 118.96, 118.52, 118.51, 117.22, 117.19, 110.67, 109.11, 73.38, 70.35, 60.76, 14.30; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, *n*-Hexane:EtOH = 7:3, 1.0 ml/min), *Rac*-**3c** t_R= 9.867 min, t_R = 29.024 min,

(*S,S)*-**3c** t_R= 9.820 min; $[\alpha]_D^{27}$ +82.7 (c = 1.0, $CHCl_3$); HRMS (ESI) calculated for $C_{25}H_{25}N_2O_5$ $[M+H]^+$: 433.1763, Found: 433.1757.

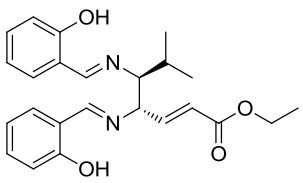
Compound (*S,S*)-**3d**



To a stirred solution of 36.6 mg (0.15 mmol) of (*R,R*)-*hpen* in 0.5 mL of DMSO (0.3 M) was added 2,6-dichlorobenzaldehyde (0.15 mmol). The resulting solution was stirred for 2 h at room temperature. The formation of imidazolidine was confirmed by taking ^{1}H NMR spectra of the reaction mixture in DMSO-d_6. 20 µL of ethyl *trans*-4-oxo-2-butenoate (0.17 mmol) was added to the reaction mixture in one portion. After stirring at room temperature for 2 h, the reaction mixture was mixed with distilled water (30 mL) and extracted with diethyl ether. The combined organic layers were washed with brine/water (1:1) three times and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with ethyl acetate / *n*-hexanes (15 %) gave the desired product. Yellow solid (78 % yield), mp 98-100 ^oC, R_f = 0.37 (*n*-Hexane:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.00 (s, 1H), 12.79 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.14 (m, 5H), 6.97 – 6.76 (m, 5H), 5.94 (dd, *J* = 15.7, 1.2 Hz, 1H), 5.57 (d, *J* = 9.3 Hz, 1H), 5.26 – 5.19 (m, 1H), 4.12 (qd, *J* = 7.1, 1.2 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.14, 167.97, 165.70, 160.98, 160.83, 143.50, 133.57, 133.21, 133.12, 132.27, 132.23, 130.89, 130.07, 129.13, 123.85, 119.17, 118.98, 118.55, 118.51, 117.11, 117.05, 73.12, 71.74, 60.70, 14.26; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, *n*-Hexane:EtOH = 7:3, 1.0 ml/min), *Rac*-**3d** t_R= 11.398 min, t_R = 13.952 min, (*S,S)*-**3d** t_R= 11.230 min; $[\alpha]_D^{27}$

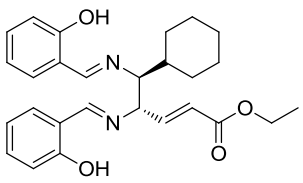
+60.2 (c = 1.0, $CHCl_3$); HRMS (ESI) calculated for $C_{27}H_{25}Cl_2N_2O_4$ $[M+H]^+$: 511.1191 , Found: 511.1167.

Compound (*S*,*S*)-**3e**



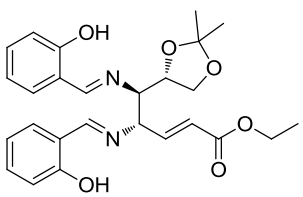
To a stirred solution of 36.6 mg (0.15 mmol) of (*R*,*R*)-*hpen* in 0.5 mL of toluene (0.3 M) was added isobutyraldehyde (0.15 mmol). The resulting solution was stirred for 1 h at room temperature. The formation of imidazolidine was confirmed by taking ^{1}H NMR spectra of the reaction mixture in DMSO-d_6. 20 µL of ethyl-*trans*-4-oxo-2-butenoate (0.17 mmol) was added to the reaction mixture in one portion. After refluxing at 110 ^{o} C for 1 h, the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with ethyl acetate / *n*-hexanes (15 %) gave the desired product. Yellow oil (62 % yield), R_f = 0.32 (*n*-Hexane:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.17 (s, 1H), 12.84 (s, 1H), 8.23 (s, 1H), 8.21 (s, 1H), 7.31 – 7.24 (m, 2H), 7.17 (ddd, *J* = 14.5, 7.7, 1.7 Hz, 2H), 7.09 (dd, *J* = 15.7, 7.2 Hz, 1H), 6.93 (dd, *J* = 8.3, 0.5 Hz, 2H), 6.85 – 6.78 (m, 2H), 6.05 (dd, *J* = 15.7, 1.2 Hz, 1H), 4.27 – 4.17 (m, 3H), 3.27 (dd, *J* = 7.4, 3.9 Hz, 1H), 2.19 – 2.07 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.85, 166.72, 165.97, 161.19, 160.98, 145.01, 132.95, 132.64, 131.94, 131.84, 123.81, 118.97, 118.80, 118.51, 118.46, 117.12, 117.03, 78.63, 72.51, 60.85, 29.42, 20.80, 16.84, 14.33; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, *n*-Hexane:EtOH = 7:3, 1.0 ml/min), *Rac*-**3e** t_R= 6.167 min, t_R = 9.981 min, (*S,S)*-**3e** t_R= 6.154 min; $[\alpha]_D^{27}$ +109.6 (c = 1.0, $CHCl_3$); HRMS (ESI) calculated for $C_{24}H_{29}N_2O_4$ $[M+H]^+$: 409.2127, Found: 409.2121.

Compound (*S,S*)-**3f**



To a stirred solution of 36.6 mg (0.15 mmol) of (*R,R*)-*hpen* in 0.5 mL of toluene (0.3 M) was added cyclohexanecarboxaldehyde (0.15 mmol). The resulting solution was stirred for 1 h at room temperature. The formation of imidazolidine was confirmed by taking ^{1}H NMR spectra of the reaction mixture in DMSO-d_6. 20 µL of ethyl-*trans*-4-oxo-2-butenoate (0.17 mmol) was added to the reaction mixture in one portion. After refluxing at 110 ^{o}C for 1 h, the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with ethyl acetate / *n*-hexanes (15 %) gave the desired product. Light yellow solid (53% yield), 147-148 ^{o}C, R_f = 0.4 (*n*-Hexane:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.23 (s, 1H), 12.87 (s, 1H), 8.23 (s, 1H), 8.18 (s, 1H), 7.31 – 7.23 (m, 2H), 7.20 – 7.13 (m, 2H), 7.09 (dd, *J* = 15.7, 7.0 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.84 – 6.78 (m, 2H), 6.03 (dd, *J* = 15.7, 1.2 Hz, 1H), 4.31 (td, *J* = 7.1, 0.9 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.25 (dd, *J* = 7.2, 4.1 Hz, 1H), 1.88 – 1.69 (m, 4H), 1.68 – 1.53 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.25 – 1.18 (m, 2H), 1.13 – 0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.83, 166.38, 166.02, 161.22, 161.00, 145.23, 132.92, 132.60, 131.92, 131.79, 123.70, 118.94, 118.77, 118.52, 118.44, 117.13, 117.05, 78.42, 71.71, 60.83, 39.14, 31.14, 27.67, 26.26, 26.26, 26.16, 14.31; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, *n*-Hexane:EtOH = 7:3, 1.0 ml/min), *Rac*-**3f** t_R= 6.707 min, t_R = 25.127 min, (*S,S)*-**3f** t_R= 6.711 min; $[\alpha]_D^{27}$ +58.8 (c = 1.0, $CHCl_3$); HRMS (ESI) calculated for $C_{27}H_{33}N_2O_4$ $[M+H]^+$: 449.2440, Found: 449.2434.

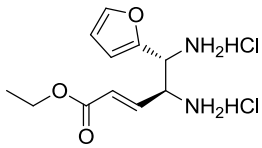
Compound (*S*,*S*)-**3g**



To a stirred solution of 36.6 mg (0.15 mmol) of (*R*,*R*)-*hpen* in 1.5 mL of toluene (0.1 M) was added (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde (0.15 mmol). The resulting solution was stirred for 2 h at room temperature. The formation of imidazolidine was confirmed by taking ^{1}H NMR spectra of the reaction mixture in DMSO-d_6. 20 µL of ethyl-*trans*-4-oxo-2-butenoate (0.17 mmol) was added to the reaction mixture in one portion. After refluxing at 110 ^{o}C for 1 h, the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with ethyl acetate / *n*-hexanes (20 %) gave the desired product. Yellow oil (50 % yield), R_f = 0.17 (*n*-Hexane:EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.00 (s, 1H), 12.76 (s, 1H), 8.26 (d, *J* = 10.4 Hz, 2H), 7.34 – 7.25 (m, 2H), 7.21 – 7.13 (m, 3H), 6.98 – 6.91 (m, 2H), 6.86 – 6.78 (m, 2H), 6.11 (dd, *J* = 15.7, 1.3 Hz, 1H), 4.43 (td, *J* = 6.7, 4.0 Hz, 1H), 4.37 (td, *J* = 6.9, 1.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.06 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.70 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.49 (dd, *J* = 7.1, 4.0 Hz, 1H), 1.49 (d, *J* = 5.2 Hz, 3H), 1.36 (s, 3H), 1.32 – 1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.06, 167.55, 165.79, 161.00, 160.78, 144.22, 133.03, 132.80, 131.94, 131.84, 124.15, 118.95, 118.69, 118.25, 118.21, 117.04, 116.98, 109.70, 74.80, 73.76, 71.64, 66.04, 60.74, 26.31, 25.26, 14.18; The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, *n*-Hexane:EtOH = 7:3, 1.0 ml/min), *Rac*-**3g** t_R= 7.950 min, t_R = 22.312 min, (*S*,*S*)-**3g** t_R= 7.561 min; $[\alpha]_D^{25}$ +87.9 (c = 1.0, $CHCl_3$); HRMS (ESI) calculated for $C_{26}H_{31}O_6N_2$ $[M+H]^+$: 467.2177, Found: 467.2160.

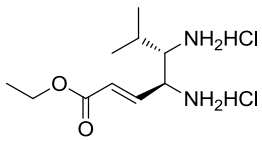
Preparation of γ,δ-diamino ester derivatives.

Compound (*S*,*S*)**-7c**



To a clear solution of **3c** (91.5 mg, 0.21 mmol) in 2.1 mL of THF (0.1 M) was added 2.5 equiv of concentrated HCl solution (44.1 µL). Stirring the reaction mixture at ambient temperature for 4 h afforded the corresponding product as a white precipitates. White solid (53.6 mg, 85 % yield); ^{1}H NMR (400 MHz, DMSO) δ 9.22 (s, 6H), 7.86 – 7.77 (m, 1H), 6.77 – 6.64 (m, 2H), 6.54 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.26 (d, *J* = 15.7 Hz, 1H), 5.11 (d, *J* = 5.8 Hz, 1H), 4.72 (dd, *J* = 7.5, 6.3 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 164.35, 144.77, 144.75, 137.09, 127.60, 112.35, 111.04, 60.58, 51.80, 48.51, 14.07; $[\alpha]_D^{25}$ +28.8 (c = 1.0, MeOH); HRMS (ESI) calculated for $C_{11}H_{17}N_2O_3$ $[M+H]^+$: 225.1239, Found: 225.1228.

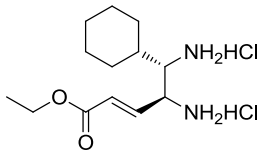
Compound (*S*,*S*)**-7e**



To a clear solution of **3e** (88 mg, 0.215 mmol) in 2.1 mL of THF (0.1 M) was added 2.5 equiv of concentrated HCl solution (45 µL). Stirring the reaction mixture at ambient temperature for 4 h afforded the corresponding product as a white precipitates. White solid (51.5 mg, 87 % yield); ^{1}H NMR (400 MHz, DMSO) δ 8.89 (s, 6H), 6.90 (dd, *J* = 15.8, 7.7 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 4.50 – 4.34 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.57 (dd, *J* = 6.0, 4.0 Hz, 1H), 2.08 – 1.94 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 164.53, 138.44, 126.56, 60.60, 56.54, 52.19, 26.77, 20.13, 16.30, 14.09; $[\alpha]_D^{24}$ -47.7

(c = 1.0, MeOH); HRMS (ESI) calculated for $C_{10}H_{21}N_2O_2$ $[M+H]^+$: 201.1603, Found: 201.1593.

Compound (*S*,*S*)**-7f**



To a clear solution of **3f** (91.5 mg, 0.21 mmol) in 2.1 mL of THF (0.1 M) was added 2.5 equiv of concentrated HCl solution (44.1 µL). Stirring the reaction mixture at ambient temperature for 4 h afforded the corresponding product as a white precipitates. White solid (85 % yield); ^{1}H NMR (400 MHz, DMSO) δ 8.90 (s, 6H), 6.91 (dd, *J* = 15.8, 7.4 Hz, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 4.48 (t, *J* = 6.2 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.53 (t, *J* = 4.6 Hz, 1H), 1.81 – 1.51 (m, 6H), 1.40 – 1.26 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.21 – 0.96 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 164.96, 138.95, 126.71, 60.97, 56.56, 52.24, 36.32, 30.16, 27.07, 26.01, 25.66, 14.50; $[\alpha]_D^{25}$ -39.3 (c = 1.0, MeOH); HRMS (ESI) calculated for $C_{13}H_{25}N_2O_2$ $[M+H]^+$: 241.1916, Found: 241.1905

Chapter III.

Stereospecific Synthesis of a Twinned Alanine Ester

III-1. Introduction

About a decade ago, resonance assisted hydrogen bond directed diaza-Cope rearrangement by Chin *et al*.[1] was pioneered for the stereospecific synthesis of chiral vicinal diamines, which had been based on the seminal works on diaza-Cope rearrangement by Vögtle and Goldschmitt.[2] Gilli *et al*. previously introduced the concept of resonance assisted hydrogen bonds (RAHBs) to demonstrate the synergistic interplay between π-delocalization and H-bonding in 2-hydroxyphenyl aldimine.[3] Since the RAHB directed DCR based on both seminal works was introduced, this method has been used for the preparation of a variety of chiral diamines[4] including C_2-symmetric aryl-[5] and alkyl-[6] substituted diamines as well as non-symmetrical chiral diamines.[7] In addition, wide ranging applications of this method have been reported including tuning

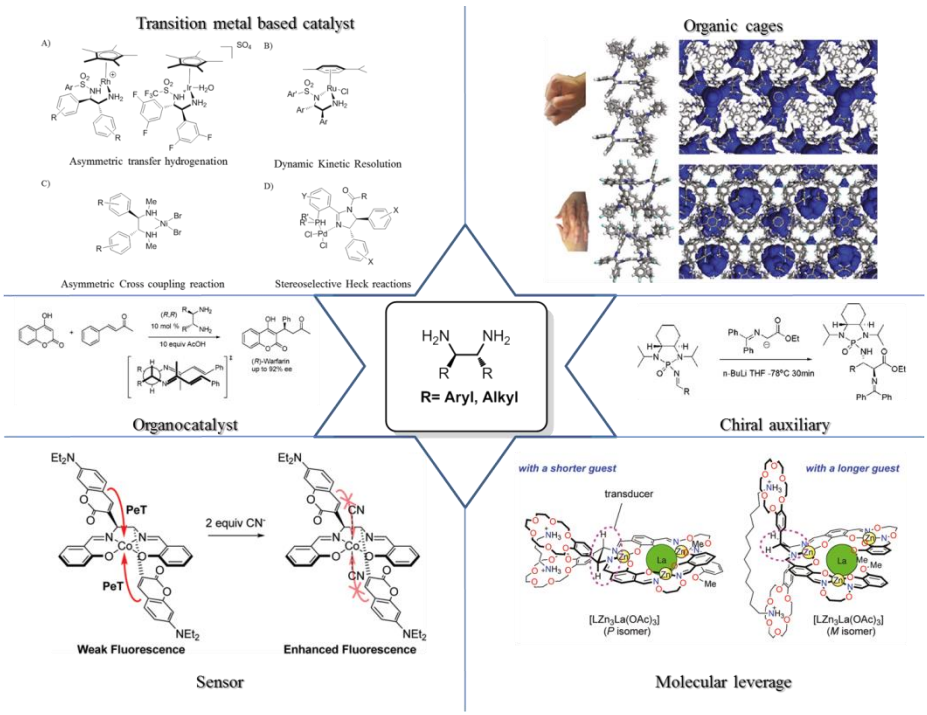
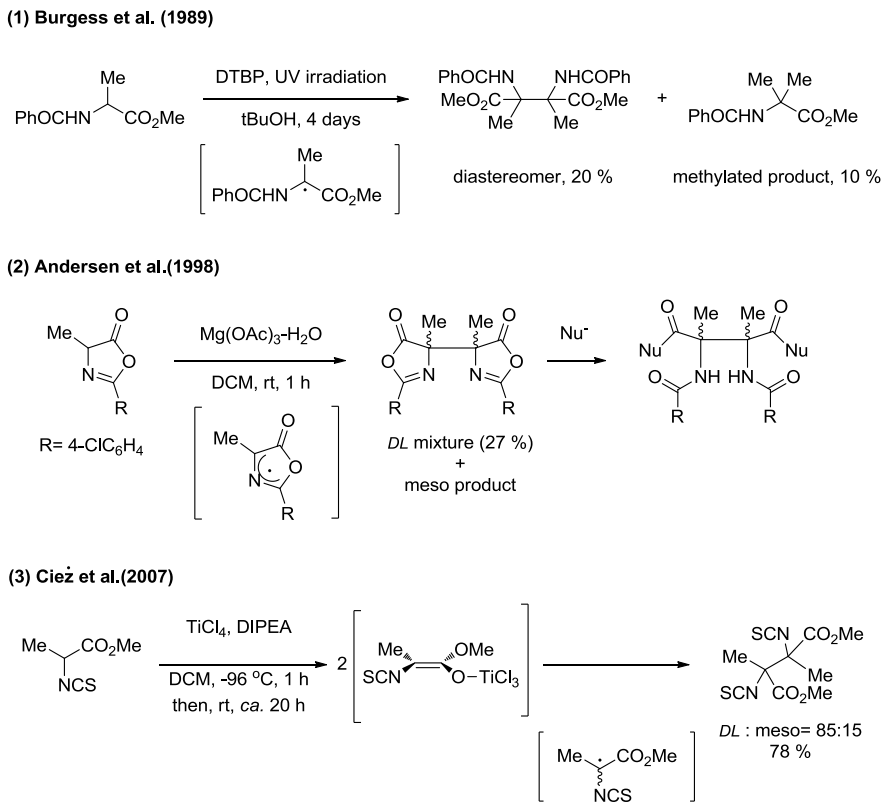


Figure III-1. Applications of Diamines Derived from *hpen*

of reactivity and stereoselectivity of transition metal based catalysts (Ir(III),[8] Ru(II),[9] reactivity Rh(II),[10] Ni(II),[11] Pd(II)[12]) and organocatalyst[13] as well as developing chiral auxiliary,[14] sensors,[15] molecular levers[16] and microporous materials (Figure III-1).[17]

In all of these rearrangement reactions, imine formation between *hpen* and aldehydes is a key reaction for the preparation of the chiral diamines. Chin *et al.* showed that mixed diimines formed between *hpen* and methyl pyruvate and aldehydes undergo diaza-Cope rearrangement to give α-substituted *syn*-α,β-diimino esters.[7b] However, it has been a challenge to obtain diaza-Cope rearrangement of diimines formed exclusively from ketones. While other interesting methods have been developed for the synthesis of twinned alanine



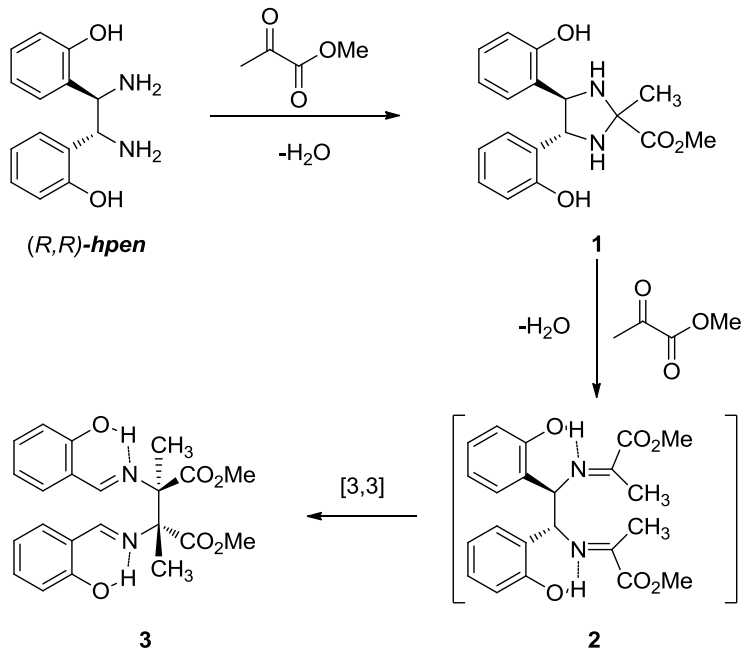
Scheme III-1. Previously Reported Synthetic Methods of Twinned Alanine Derivatives.

derivatives,[18] stereospecific versions have not been reported (Scheme III-1).

Here we report the first such example using methyl pyruvate as the ketone for stereospecific synthesis of a twinned alanine ester with two quaternary chiral centers. DFT computation provides interesting insights into the origin of stereospecificity as well as the rate and equilibrium constants for the facile rearrangement reaction.

III-2. Result and Discussion

In a typical experiment, (*R,R*)-*hpen* (0.50 g) was added to neat methyl pyruvate (2.0 mL, *approx.* 10 equiv) and the mixture was stirred at ambient temperature for 14 h (Scheme III-2).



Scheme III-2. Stereospecific Synthesis of Twinned Alanine Ester.

The crude product (**3**) was purified by column chromatography followed by crystallization. ^{1}H NMR of the crude product in $CDCl_3$ shows that the diastereomeric purity of **3** is over 94%. The enantiopurity of **3** (>99% ee) is greater than its diastereopurity as determined by chiral HPLC analysis and also as expected from the computational studies shown below. The crystal structure of **3** reveals that the two chiral centers are both *R* in configuration (Figure III-3). Thus the diaza-Cope rearrangement with diimines formed from methyl pyruvate and *hpen* takes place stereospecifically as it does with diimines formed from aldehydes and *hpen*.

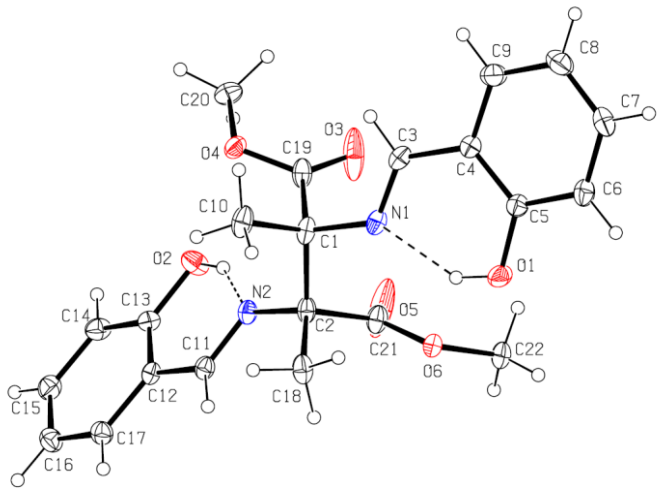


Figure III-2. Crystal Structure of Chiral Diimine **3.**

Time dependent ^{1}H NMR shows that the one pot reaction for formation of **3** from *hpen* and methyl pyruvate proceeds by initial formation of the imidazolidine intermediate (**1**) that can be isolated. This five-membered ring forms cleanly within 2 h from the reaction of *hpen* and methyl pyruvate. The aminal carbon in the five-membered ring is not a stereogenic center due to the pseudo C_2 symmetry of **1**. Reaction of the imidazolidine ring with a second equivalent methyl pyruvate apparently gives the initial diimine (**2**) that

rearranges to give **3**.

It is generally difficult to obtain diaza-Cope rearrangement of diimines formed between *hpen* and ketones as this will result in formation of sterically hindered diimines with two quaternary carbons attached to each other. Furthermore, controlling stereospecificity for the rearrangement is considerably more challenging with diimines formed with ketones than those formed with aldehydes. Interestingly, diimines formed from *hpen* and methyl pyruvate undergo diaza-Cope rearrangement smoothly and cleanly at ambient temperature with excellent stereospecificity. The diaza-Cope rearrangement of the diimine formed between *hpen* and methyl pyruvate is expected to go through a six-membered ring transition state **4a**, **4b** or **4c** (Figure III-3).

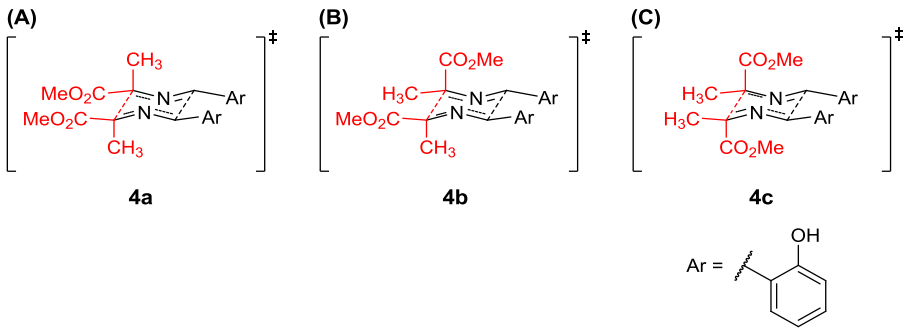


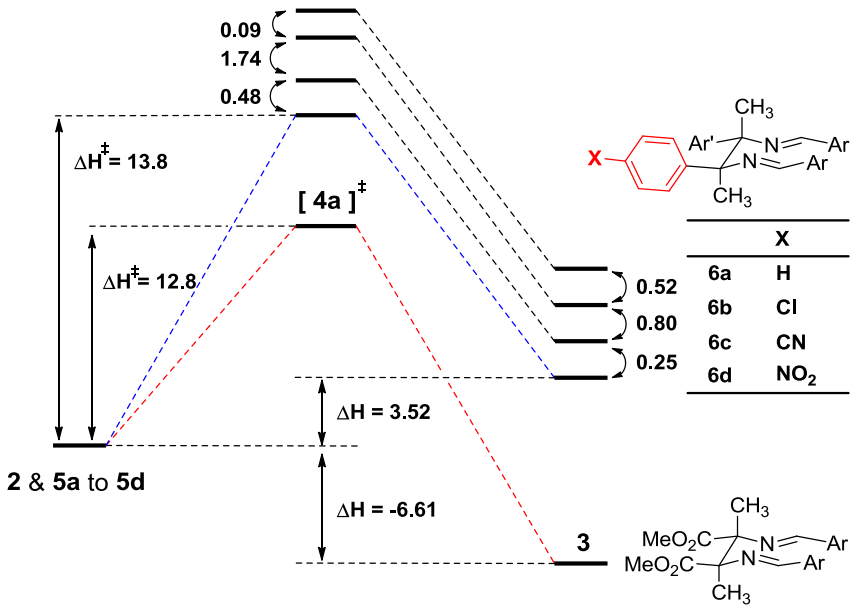
Figure III-3. Transition States of **4**. (A) Both carboxylate groups in equatorial position (**4a**). (B) One carboxylate group in equatorial position, the other in axial position (**4b**). (C) Both carboxylate groups in axial position (**4c**).

DFT computation (B3LYP at the 6-31G* level)[19] shows that **4a** is the most stable followed by **4b** ($\Delta\Delta H^{\ddagger}$ = 1.49 kcal/mol) and **4c** ($\Delta\Delta H^{\ddagger}$ = 2.63 kcal/mol). The most stable transition state (**4a**) with both carboxylate groups in equatorial positions leads to formation of the product diimine with (*R*,*R*) configuration (**3**) as observed experimentally through X-ray crystallography (Figure III-1) and chiral HPLC analysis. The second most stable transition

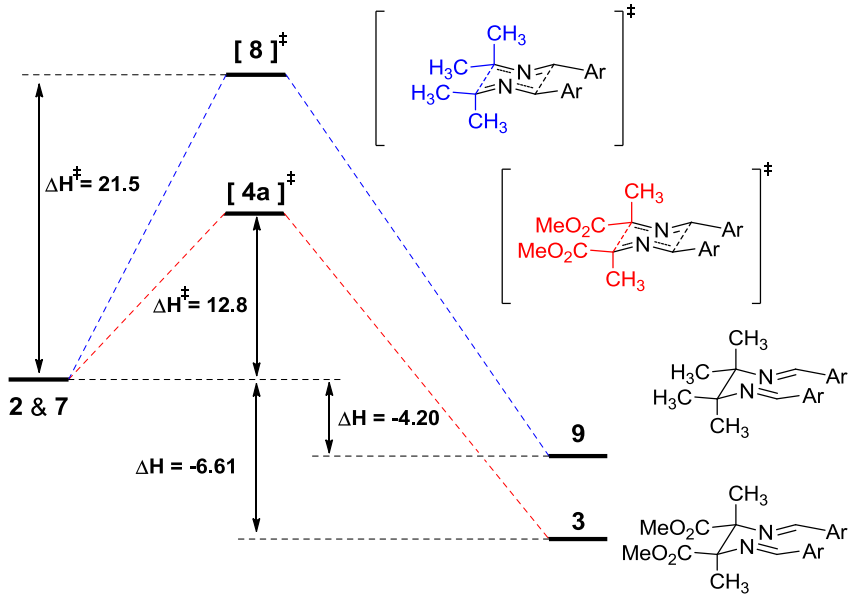
state (**4b**) leads to formation of the *meso* diimine product. The above transition state energy difference (1.49 kcal/mol) translates to formation of about 10% of the diimine in the *meso* form. Consistent with computation, ^{1}H NMR of the crude rearrangement product indicates that about 3% of the rearranged diimine appears to be in the *meso* form. The least stable transition state (**4c**) with both carboxylate groups in axial positions leads to formation of the diimine product with (*S*,*S*) configuration. DFT computation shows that the amount of the (*S*,*S*)-enantiomer formed from the least stable transition state ($\Delta\Delta H^{\ddagger}$ = 2.63 kcal/mol) would be less than 2%. Consistent with computation, we do not observe any of the (*S*,*S*)-enantiomer through chiral HPLC analysis. X-ray crystallography was used to determine the product configuration.

The energies of the initial diimines leading to transitions states **4a**, **4b** and **4c** are provided in the Appendix C. If the starting E and Z diimines are in rapid equilibrium, only the transition state energies determine the product distribution according to the Curtin-Hammett principle.[20]

We have not been able to synthesize the analogous diimines using *hpen* and acetone or acetophenone in place of methyl pyruvate. DFT computation provides some interesting insights into why methyl pyruvate is a particularly useful ketone for the rearrangement reaction. Rearrangement of **2** to **3** (Scheme III-2) is a downhill reaction (ΔH = -6.61 kcal/mol) with a relatively low energy barrier ($\Delta H^{\ddagger}$ = 12.8 kcal/mol). By comparison, rearrangement of the diimine formed between *hpen* and acetophenone (**5a**) to form the product diimine (**6a**) is an uphill reaction (ΔH = 5.09 kcal/mol, Scheme III-3). This thermodynamic barrier can be lowered with electron withdrawing substituents such as chloro (ΔH = 4.56 kcal/mol, **5b**), cyano (ΔH = 3.77 kcal/mol, **5c**) or nitro (ΔH = 3.52 kcal/mol, **5d**) groups. However, none of these reactions with substituted acetophenones are thermodynamically downhill reactions as the one with methyl pyruvate.



Scheme III-3. Comparison of Energy Barrier Following *p*-Substituents on Acetophenones (Energy values in kcal/mol).[19]

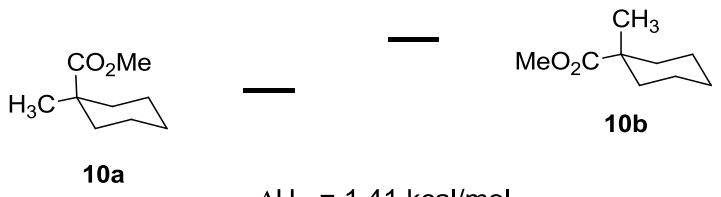


Scheme III-4. Comparison of Diimine Formation From *hpen* with Acetone/Methyl Pyruvate (Energy values in kcal/mol).[19]

While rearrangement of diimine formed between *hpen* and acetone (**7**) is thermodynamically favorable (ΔH = -4.20 kcal/mol, Scheme III-4), it has a relatively large energy barrier to form the product diimine (**9**). The energy barrier for formation of **9** is about 8.68 kcal/mol greater than that for the rearrangement of the diimine formed with *hpen* and methyl pyruvate (**2**). The greater energy barrier translates to about 2 x 10^6-fold decrease in rate at room temperature. This slowing down of the rearrangement reaction may be due to the unfavorable steric effects of four sp^3 hybridized carbon atoms (methyl groups) coming together at the transition state.

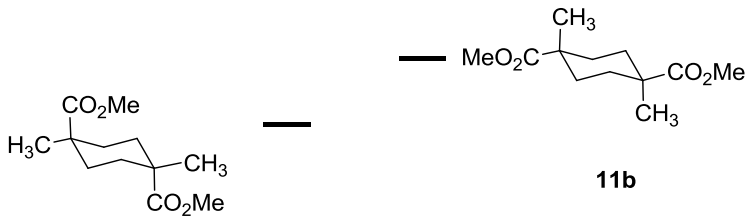
Toward a better understanding of the relationship between the experimental data and calculation results, further conformational study has been investigated. In organic chemistry textbooks, the 1,3-diaxial strain is greater for methane than for esters,[21] Thus it should be better to have the ester in the axial position than the methyl. However, we need to be careful when extending this to systems with many substituents.

DFT computation (B3LYP at the 6-31G* level) shows that **10a** is more stable than **10b** as expected from the individual 1,3-diaxial strain.



10a **10b**

ΔH_{10}= 1.41 kcal/mol

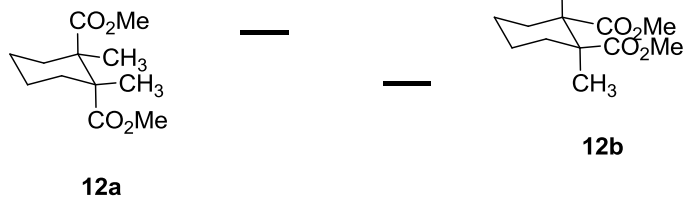


11a **11b**

ΔH_{11}= 3.48 kcal/mol

Furthermore, computation shows that **11a** is more stable than **11b** as expected from above conformation **10.**

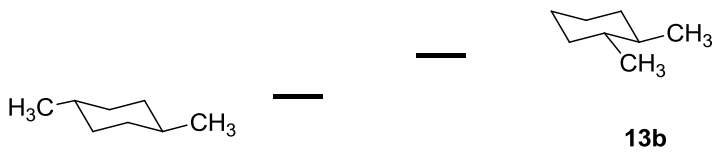
However, when we bring the substituents closer together the trend of energy difference is reversed. Here it is better to have the carboxylates together in the equatorial positions as in **12b** than to have the methyl groups together in the equatorial positions as in **12a**.



12a **12b**

ΔH (**12**)= -1.31 kcal/mol

Further analysis below shows that it is energetically better to have carboxylates together than to have methyl groups together on equatorial positions in 1,2-disubstituted cyclohexanes. Computation predicts that 1,2-dimethyl cyclohexane (**13b**) is less stable than 1,4-dimethyl cyclohexane (**13a**) due apparently to greater steric effect (gauche interaction) when the two methyl groups are closer.



13a **13b**

ΔH (**13**) = 1.03 kcal/mol

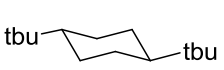
The gap is reduced significantly for the dicarboxylates. Indeed, the 1,2-disubstituted carboxylate (**14b**) is more stable than the 1,4-disubstituted one (**14a**). Thus there appears to be even energetically favorable interactions between the two carboxylates.

14a **14b**

ΔH (**14**)= 0.61 kcal/mol

The energy gap becomes much bigger in case of the *t*-butyl substituent because of the bulkiness as shown below (**15a** and **15b**).

15b



15a

ΔH (**15**)= 21.7 kcal/mol

III-3. Conclusion

A diamino diacid with two quarternary chiral centers has been synthesized with excellent stereospecificity under mild conditions by diaza-Cope rearrangement. This represents the first time a ketone has been used exclusively for the rearrangement reaction. DFT computation shows that the rearrangement is thermodynamically more favorable with electron deficient ketones like methyl pyruvate over acetophenones. Furthermore, the rearrangement is kinetically more favorable with conjugated ketones like methyl pyruvate over alkyl ketones due to greater steric crowding at the transition state in the latter case. Additionally, conformational study shows that it is more favourable to have both carboxylates together than to have both methyl groups on the equatorial position, resulting in the choice of transition state **4a** and the production of compound **3**.

III-4. Experimental

General Information

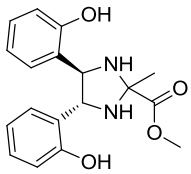
Commercially available compounds were used without further purification or drying. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer or a Bruker Advance III 400 MHz spectrometer. High resolution mass spectra (HRMS) were obtained on an ABI/Sciex QStar Mass Spectrometer (ESI) at Advanced Instrumentation for Molecular Structure (AIMS) at the University of Toronto and on a ThermoFinnigan LCQ™ Classic, Quadrupole Ion-Trap Mass Spectrometer at Seoul National University. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC, UV detection monitored at 254.4 nm using a Chiralpak® IA column (25cm). Optical rotation was obtained at 589 nm using a Rudolph Autopol IV polarimeter at the University of Toronto and on a JASCO P-1030 automatic polarimeter at Seoul National University. Melting points were recorded using an Electrothermal IA 9100 digital melting point apparatus. Reactions were monitored using ^{1}H NMR spectroscopy. Chromatography was performed on Silicycle 230-400 mesh silica gel and thin-layer chromatography (TLC) was performed on EMD Silica Gel 60 F_{254} plates. Visualization of the developed plates was performed under UV light (254 nm). All calculations were performed using Spartan ‘08 for Windows from Wavefunction Inc.

Preparation of 5-membered imidazolidine intermediate (1)

After adding methyl pyruvate (407 μL, 4.51 mmol) to (*R*,*R*)-1,2-bis(2-hydroxylphenyl)-1,2-diaminoethane (1.0 g, 4.1 mmol) in $CHCl_3$, the reaction mixture was stirred at 50 ^{o}C for 1 h until starting material was all removed. The solvent was removed *in vacuo* and 2 mL of diethyl ether was added to afford a desired product and 5 mL of *n*-hexane was added to reduce the loss of isolated yield. The solid was

filtered, washed with 10 mL of *n*-hexane, and dried in vacuum. The desired product was obtained as light yellow solid (1.25 g, 93% yield).

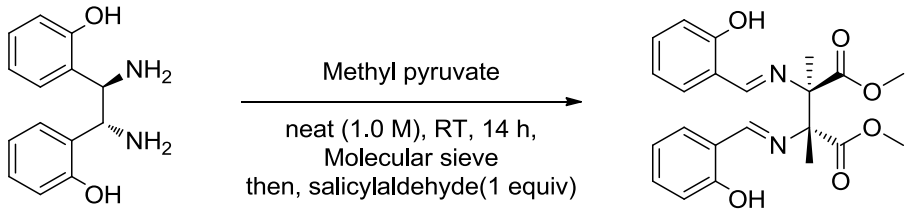
Compound (*R,R*)-**1**



Light yellow solid (93% yield), mp 137-138 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.74 (s, 2H), 7.23 – 7.08 (m, 2H), 6.92 – 6.80 (m, 2H), 6.61 (td, *J* = 7.4, 1.1 Hz, 1H), 6.56 (td, *J* = 7.5, 1.1 Hz, 1H), 6.33 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.20 (dd, *J* = 7.6, 1.5 Hz, 1H), 4.64 (d, *J* = 9.7 Hz, 1H), 4.36 (d, *J* = 9.8 Hz, 1H), 3.91 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 157.5, 157.3, 130.0, 129.7, 129.5, 129.3, 119.5, 119.4, 119.1, 118.9, 117.2, 117.0, 76.4, 67.4, 66.1, 53.6, 27.3. $[\alpha]_D^{24}$ +6.51 (c = 1.0, $CHCl_3$). HRMS (ESI) calculated for $C_{18}H_{21}N_2O_4$ $[M+H]^+$: 329.1501, Found: 329.1494

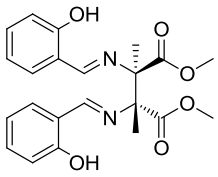
Preparation of chiral diimine containing vicinal quaternary carbon centers (3)



After adding methyl pyruvate (2.05 mL, 1.0 M) with activated molecular sieve (3 Å) to *(R,R)*-1,2-bis(2-hydroxylphenyl)-1,2-diaminoethane (0.50 g, 2.05 mmol) in $CHCl_3$, the mixture was stirred at room temperature for 14 h until 5-membered ring was all removed. Salicylaldehyde (218 μL, 2.05 mmol) was added to the reaction mixture and the mixture was stirred at room temperature for 1 h. The reaction mixture was purified using short column chromatography eluting with hexane / ethyl acetate (20 %) to remove excess methyl pyruvate and salicylaldehyde. Recrystallization of obtained

crude product in diethyl ether / *n*-hexane gave the desired product as a yellow monoclinic crystal (60% yield).

Compound (*R,R*)-**3**



Yellow monoclinic crystal (60% yield), mp 115-116 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.98 (s, 1H); 8.39 (s, 1H; 7.34 (t, *J* = 7.8 Hz, 1H); 7.28 (d, *J* = 7.6 Hz, 1H); 6.98 (d, *J* = 8.4 Hz, 1H); 6.89 (t, *J* = 7.5 Hz, 1H); 3.76 (s, 3H); 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.0, 165.2, 161.1, 133.2, 132.4, 119.0, 118.9, 117.5, 73.6, 53.0, 19.3. The enantiopurity was confirmed by HPLC analysis (Chiralpak® IA column, *n*-Hexane:*i*-PrOH = 90:10, 1.0 ml/min); *Rac*-**3** t_R= 8.96 min, t_R = 16.34 min, (*R,R*)-**3** t_R= 16.32 min, (*S,S*)-**3** t_R= 8.98 min. $[\alpha]_D^{27}$ +175.95 (c = 1.0, $CHCl_3$). HRMS (ESI) calculated for $C_{22}H_{25}N_2O_6$ $[M+H]^+$: 413.1713, Found: 413.1707.

Chapter IV.

Sugar as Chiral Derivatizing Agent for the Determination of the Enantiopurity of Vicinal Diamines

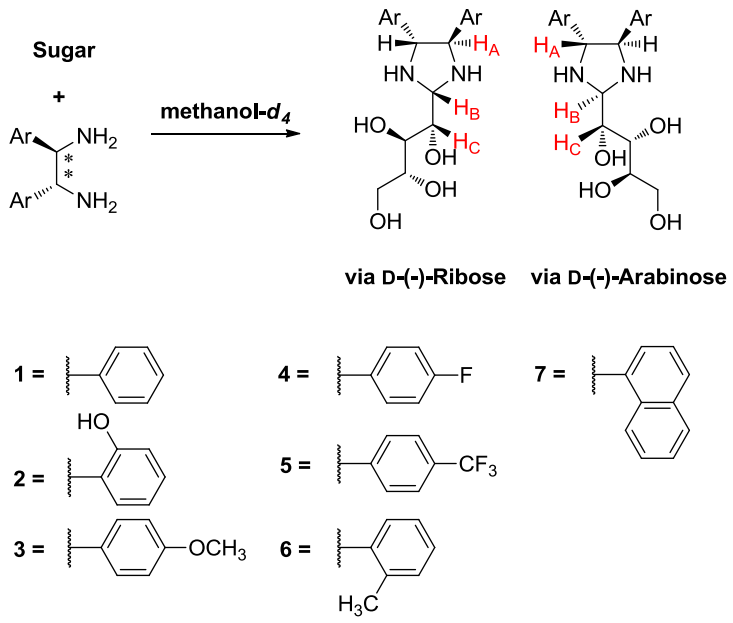
IV-1. Introduction

We have demonstrated the importance and usefulness of chiral vicinal diamines in previous Chapters. As a result, there has been much interest in developing stereoselective methods for the preparation of C_2-symmetric diamines[1] as well as in developing convenient methods for determining their enantiopurity.[2] NMR spectroscopic analysis has emerged as a quite useful tool for the determination of enantiopurities and absolute configurations of various chiral compounds. Many NMR analysis methods have been recently developed[3] as interesting chiral derivatizing agents (CDAs) and chiral shift reagents (CSAs) for determining the enantiopurities of carboxylic acids,[4] alcohols,[5] cyanohydrin[6] and amines.[7] In general, CSAs are more convenient to use since prior derivatization is not required as with most CDAs. Elegant macrocyclic CSAs that rely on hydrogen bonding have been developed.[8] However, they are more difficult to synthesize than typical CDAs. An innovative alternative is to have easy to make CDAs that rely on reversible covalent bonds such as imines.[9] Thus chiral aldehydes are potentially valuable as CDAs for determining the enantiopurity of primary amines.[10] To the best of our knowledge, we found one literature example for using aldehydes for determining the enantiopurity of a protection-free C_2-symmetric vicinal diamine.[11] In that interesting study, binol and 2-formylphenylboronic acid[12] was used as CDA to determine the enantiopurity of diphenylethylenediamine (*dpen*). Sugars are some of the cheapest and most readily available chiral aldehydes known and have been popular as chiral building blocks for developing drugs and catalysts.[13] Here we report the use of ribose and arabinose as CDAs for the determination of the enantiopurity of C_2-symmetric chiral diamines including *dpen*.

IV-2. Result and Discussion

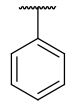
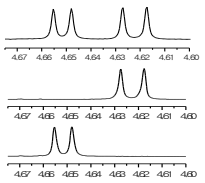
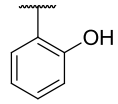
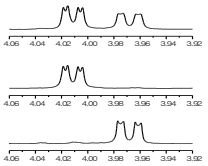
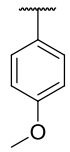
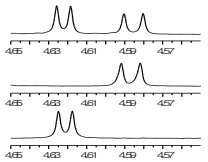
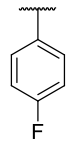
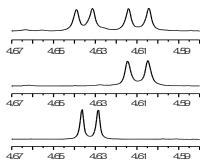
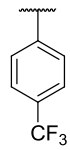
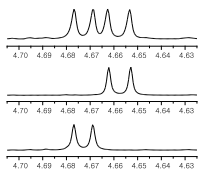
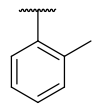
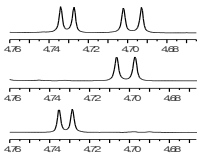
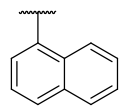
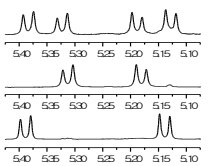
Diamines react with aldehyde in ribose or arabinose to form imidazolidines. There are three ^{1}H NMR signals (H_A, H_B and H_C) in the imidazolidines that may be used for determining the enantiopurity of diamines (Scheme IV-1). In a typical experiment, vicinal diamine (0.035 mmol) was added to 1.3 equiv of D-ribose or D-arabinose in methanol-d_4 (0.7 ml) and stirred for 5 h at 50 ^{o}C to afford the corresponding imidazolidine. Excess sugar was used to drive the reaction to completion and prevent kinetic effects. ^{1}H NMR shows that diimine formation or diaza-Cope rearrangement[1i] do not take place under our experimental conditions.

In order to study the scope of our protocol, a series of C_2-symmetric diamines were tested. The resulting ^{1}H NMR spectrum and the difference in chemical shifts (δ) of the diastereomers for each of the diamines are summarized in Table IV-1.



Scheme IV-1. Imidazolidines from Diamines and Sugars.

Table IV-1. Chemical Shift Differences (Δδ) in the 400 MHz ^{1}H NMR Spectra in MeOH-d_4[a]

Entry	Diamine (Ar)	Sugar	Peak (Δδ)[b]	Spectra[c]
1		Ribose	H_B (0.029)	
2		Arabinose	H_C (0.045)	
3		Ribose	H_B (0.037)	
4		Ribose	H_B (0.026)	
5		Ribose	H_B (0.015)	
6		Ribose	H_B (0.033)	
7		Ribose	H_A (0.061)	

[a] Reagents and condition: diamines (0.035 mmol), methanol-d_4 (0.7 mL, 0.05 M), sugar (0.046 mmol), 50 °C, 5 h.
[b] Chemical shift difference.
[c] Racemic mixture (top)/(*R*,*R*)-form (middle)/(*S*,*S*)-form. (bottom)

In cases of diamines **1**, **3**, **4**, **5** and **6**, the H_B doublet signal from the imidazolidine formed with D-ribose was used to determine the enantiopurity of the diamines. In each of these imidazolidines, the H_B signals obtained with the (*R,R)*-diamines appeared upfield of those obtained with the (*S,S)*-diamines. For diamine **2**, best resolution was obtained with the H_C signal of the imidazolidine formed with D-arabinose. In case of **7**, the H_A signal of the imidazolidine formed with D-ribose was used to determine the enantiopurity. The two H_A signals in the imidazolidine ring are different and appear as an

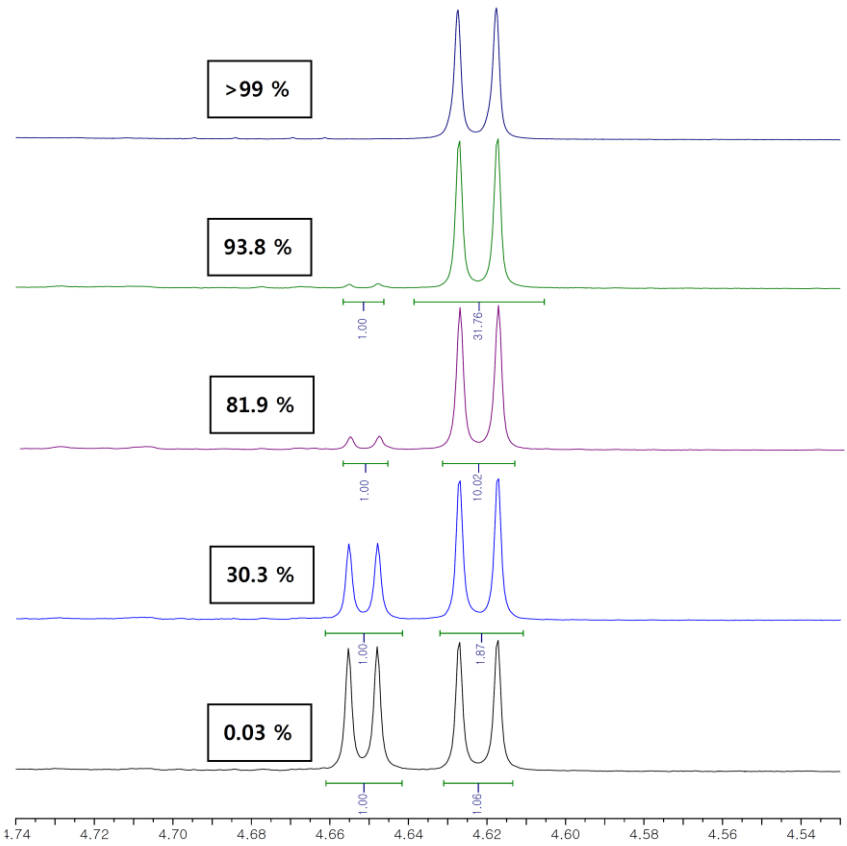


Figure IV-1. Expansion of the Aminal Proton Region of ^{1}H NMR Enantiomerically Mixed *dpen* and D-(-)-ribose.

AB signal. Our method did not work for determining the enantiopurity of 1,2-diaminocyclohexane (*dach*). D-ribose or D-arabinose does not cleanly form imidazolidine ring with *dach* due to ring strain.[11]

We tested the reliability of our sugar-based CDA-NMR protocol using samples of **1** with known enantiopurities (0, 32, 81, 94 and >99% ee *RR*-**1**). There is excellent agreement between the enantiopurities determined using our protocol and the known enantiopurities of **1** as shown in Figure IV-1. We also determined the enantiopurities of **1** using chiral HPLC analysis. For the preparation of each samples, we used the diaza-Cope rearrangement to synthesize product diimines, followed by hydrolysis of the product diimines and subsequent neutralization. The enantiopurity of each sample was confirmed by chiral HPLC analysis at the diimine stage (Chiralpak® IA column, *n*-hexane:*iso*-propyl alcohol = 9:1, 1.0 ml/min). There is also an excellent agreement between our sugar-based CDA-NMR and the chiral HPLC methods for determining the enantiopurities of **1** (Figure IV-2).

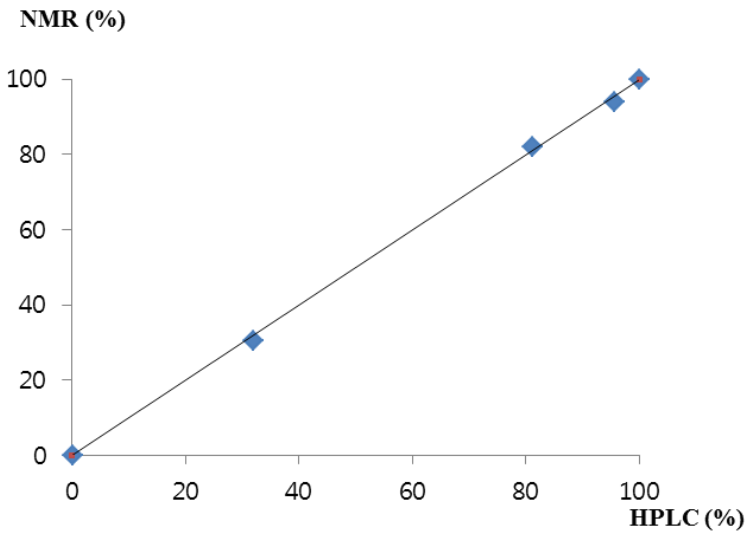


Figure IV-2. The Degree of Linearity between NMR and Chiral HPLC Analyses.

Our sugar-based protocol for determining the enantiopurity of vicinal diamines provides error limits well within the accepted 2% range for ^{1}H NMR (Table IV-2).[14]

Table IV-2. Comparison of NMR Spectra and HPLC Analysis.

HPLC (% ee)	CDA (% ee)
0.3	0.03
32	30.3
81.2	81.9
95.7	93.8
>99	>99

IV-3. Conclusion

We have shown that readily available sugar molecules can be used as chiral derivatizing agents for determining the enantiopurity of a range of vicinal diamines. This ^{1}H NMR method is simple and convenient and does not require any prior derivatization of the sugar or the diamine. The accuracy of this protocol has been confirmed by HPLC methods.

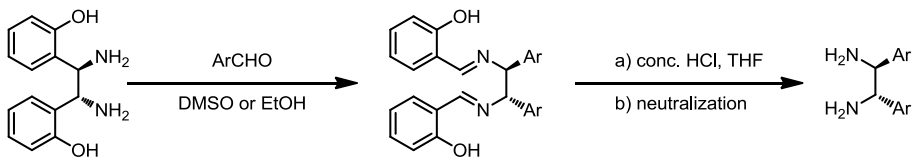
IV-4. Experimental

General Information

All materials were obtained from commercial supplier and used without further purification. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on an Agilent DD2MR400 400 MHz spectrometer in Seoul National University (SNU) and the NMR solvent (methanol-d_4) was from Cambridge Isotope Laboratories, Inc. High resolution mass spectra (HRMS) were obtained on a ThermoFinnigan LCQ™ Classic, Quadrupole Ion-Trap Mass Spectrometer. Chiral HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC, UV detection monitored at 254.4 nm using a Chiralpak® IA column (25cm).

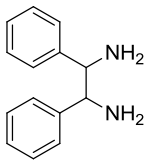
Preparation of chiral diamines

All diamines were prepared through diaza-Cope rearrangement (DCR) with (*R,R*)/(*S,S*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (*hpen)* following Chin's previous paper (*J. Am. Chem. Soc.* **2008**, *130,* 12184). And the neutralization of chiral diamine dihydrochloride was performed with 10N NaOH, followed by filteration or extraction with chloroform to obtain desired products.



Compound 1

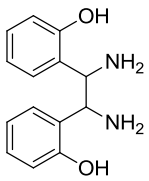
(*R*,*R*)/(*S*,*S*)-1,2-diphenyl-1,2-diaminoethane



^{1}H NMR (400 MHz, CD_3OD) δ 7.23 – 7.05 (m, 10H), 3.96 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 143.80, 129.12, 128.38, 128.05, 63.86. HRMS (ESI) calculated for $C_{14}H_{17}N_2$ $[M+H]^+$: 213.1392, Found: 213.1383

Compound 2

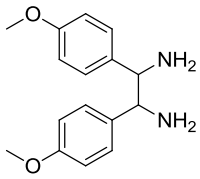
(*R*,*R*)/(*S*,*S*)-1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane



^{1}H NMR (400 MHz, CD_3OD) δ 6.99 (td, *J* = 8.0, 1.7 Hz, 2H), 6.81 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.71 (dd, *J* = 8.1, 1.0 Hz, 2H), 6.57 (td, *J* = 7.4, 1.1 Hz, 2H), 4.30 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 157.53, 130.19, 129.23, 129.11, 119.87, 117.42, 60.60. HRMS (ESI) calculated for $C_{14}H_{17}N_2$ $[M+H]^+$: 245.1290, Found: 245.1278

Compound 3

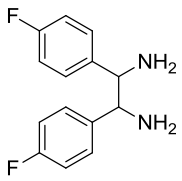
(*R*,*R*)/(*S*,*S*)-1,2-bis(4-methoxyphenyl)-1,2-diaminoethane



^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 8.7 Hz, 4H), 6.74 (d, *J* = 8.7 Hz, 4H), 3.88 (s, 2H), 3.71 (s, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 160.09, 135.84, 129.41, 114.44, 63.26, 55.55. HRMS (ESI) calculated for $C_{14}H_{17}N_2$ $[M+H]^+$: 273.1603, Found: 273.1590

Compound 4

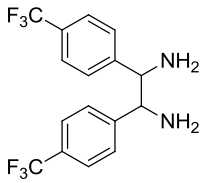
(*R*,*R*)/(*S*,*S*)-1,2-bis(4-fluorophenyl)-1,2-diaminoethane



^{1}H NMR (400 MHz, CD_3OD) δ 7.11 (dd, *J* = 8.7, 5.4 Hz, 4H), 6.90 (t, *J* = 8.8 Hz, 4H), 3.92 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 164.44, 162.01, 139.87, 139.84, 130.21, 130.13, 115.83, 115.61, 63.42. ^{19}F NMR (376 MHz, CD_3OD) δ -117.82. HRMS (ESI) calculated for $C_{14}H_{17}N_2$ $[M+H]^+$: 249.1203, Found: 249.1193

Compound 5

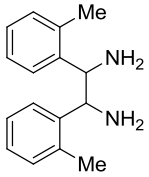
(*R*,*R*)/(*S*,*S*)-1,2-bis(4-trifluoromethylphenyl)-1,2-diaminoethane



^{1}H NMR (400 MHz, CD_3OD) δ 7.11 (dd, *J* = 8.7, 5.4 Hz, 4H), 6.90 (t, *J* = 8.8 Hz, 4H), 3.92 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 146.92, 129.05, 128.73, 127.68, 125.52, 124.65, 124.61, 124.57, 124.54, 122.82, 62.15. ^{19}F NMR (376 MHz, cd_3od) δ -64.05. HRMS (ESI) calculated for $C_{14}H_{17}N_2$ $[M+H]^+$: 349.1139, Found: 349.1124

Compound 6

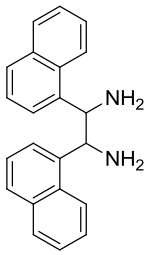
(*R*,*R*)/(*S*,*S*)-1,2-bis(2-methylphenyl)-1,2-diaminoethane



^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.14 (td, *J* = 7.5, 0.9 Hz, 2H), 7.02 (td, *J* = 7.5, 1.4 Hz, 2H), 6.93 – 6.83 (m, 2H), 4.27 (s, 2H), 1.94 (s, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 142.31, 136.74, 131.11, 127.92, 127.50, 126.97, 58.22, 19.62. HRMS (ESI) calculated for $C_{14}H_{17}N_2$ $[M+H]^+$: 241.1705, Found: 241.1695

Compound 7

(*R*,*R*)/(*S*,*S*)-1,2-dinaphthyl-1,2-diaminoethane



^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.67 (dd, *J* = 16.2, 7.4 Hz, 4H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.47 – 7.27 (m, 6H), 5.10 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 138.83, 133.74, 130.84, 128.29, 127.15, 125.34, 124.84, 124.73, 123.75, 122.52, 55.60. HRMS (ESI) calculated for $C_{14}H_{17}N_2$ $[M+H]^+$: 313.1705, Found: 313.1691.

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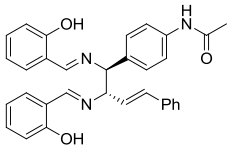
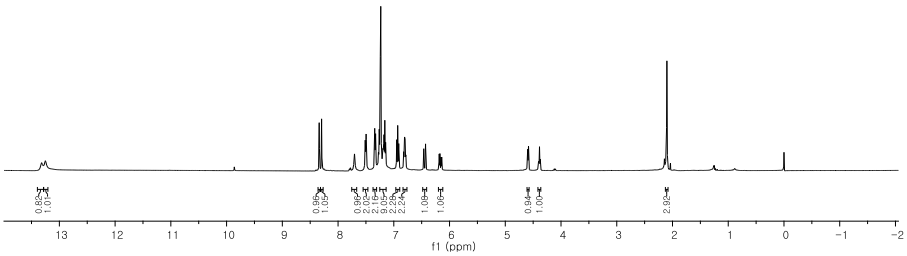
Appendix A

NMR spectra

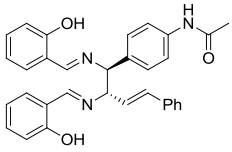
Chapter 1.



(*S*,*S*)-**4j**



^{1}H NMR spectrum of **4j** (500 MHz, $CDCl_3$)



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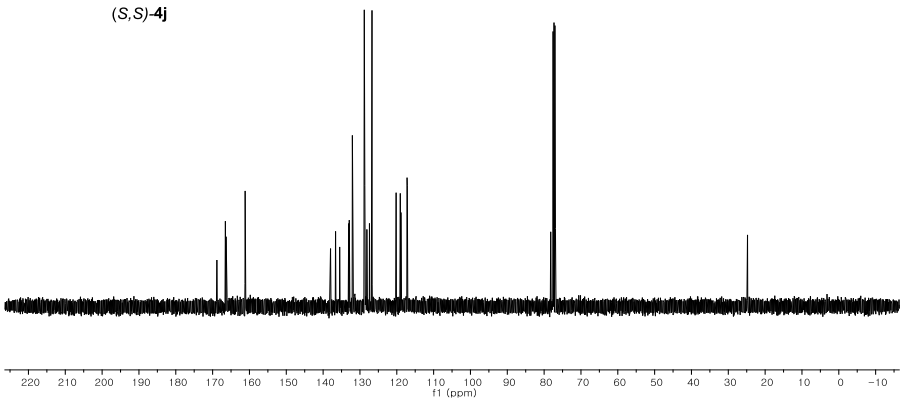
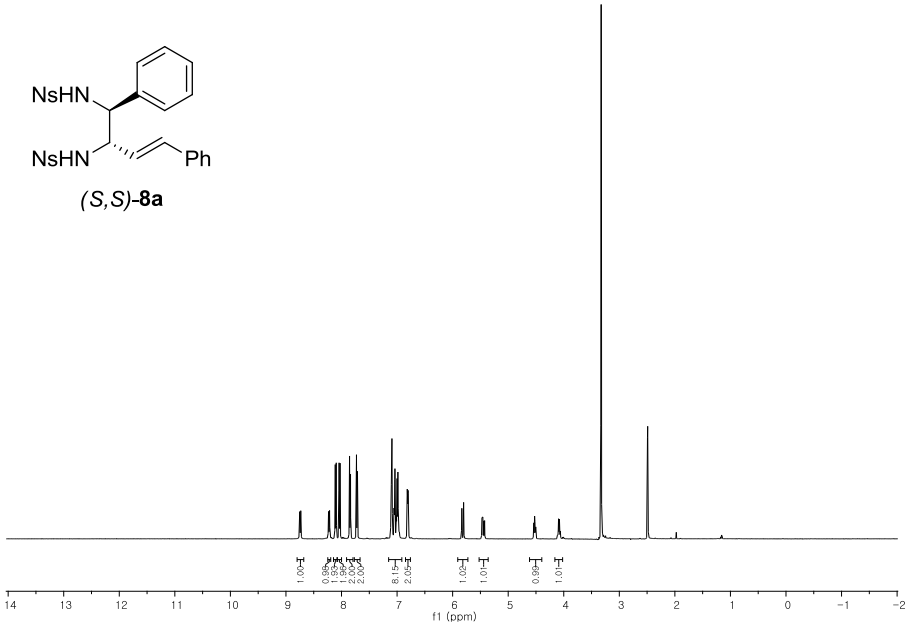
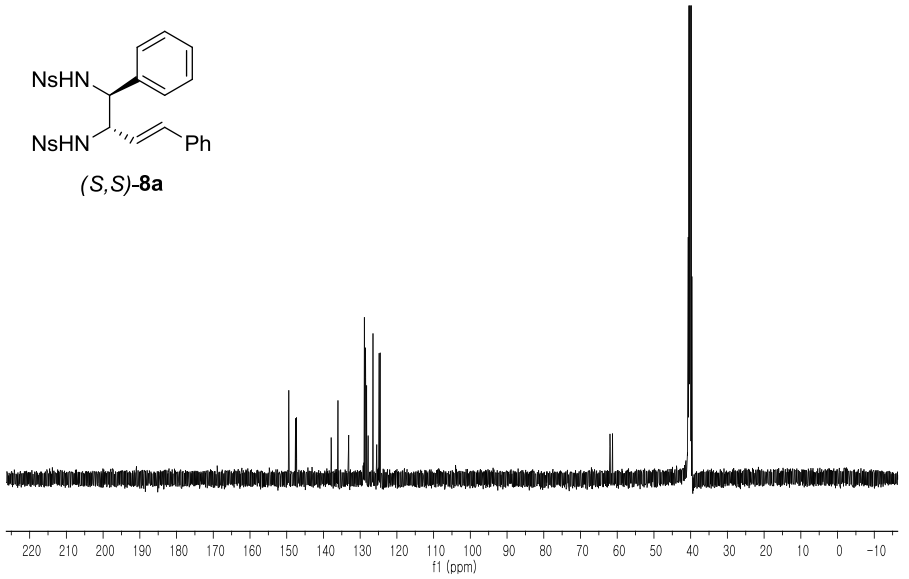


^{13}C NMR spectrum of **4j** (126 MHz, $CDCl_3$)



^{1}H NMR spectrum of **8a** (500 MHz, DMSO-d_6)



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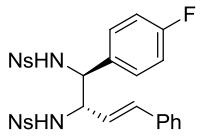

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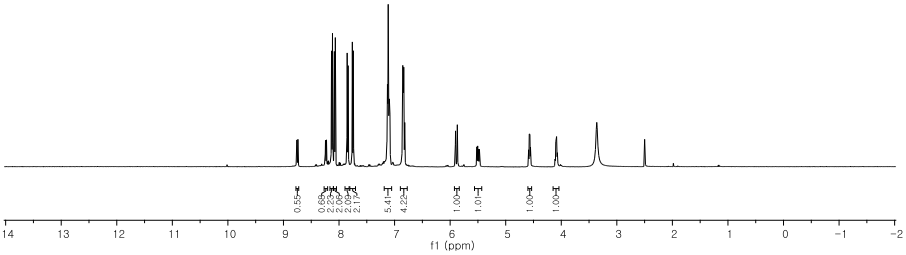
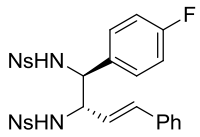
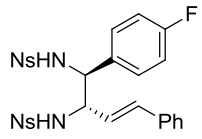


^{1}H NMR spectrum of **8b** (500 MHz, DMSO-d_6)



(*S*,*S*)-**8b**

^{13}C NMR spectrum of **8a** (75 MHz, DMSO-d_6)



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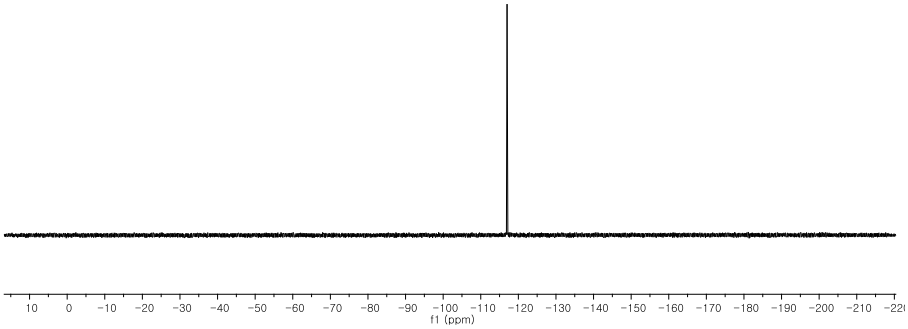
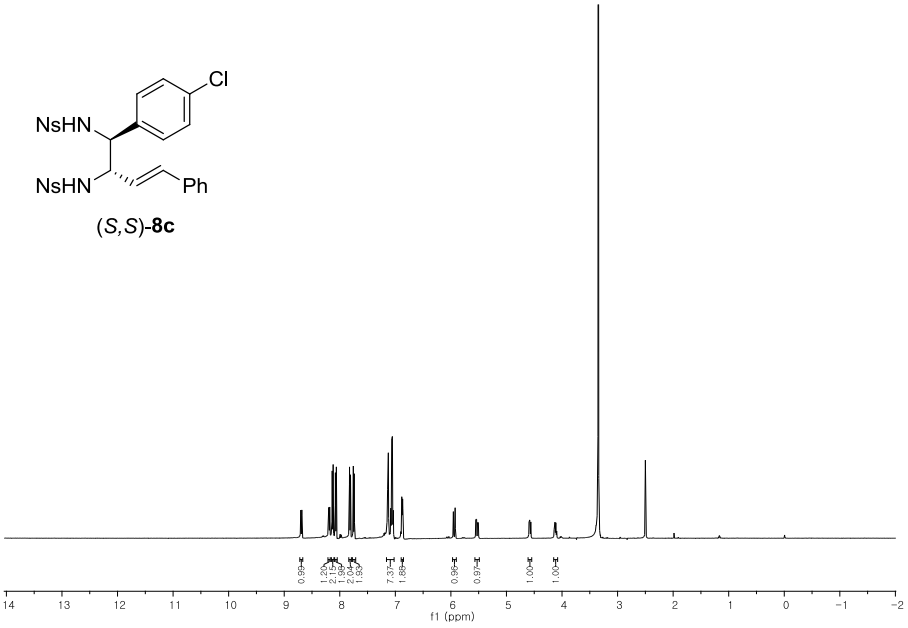
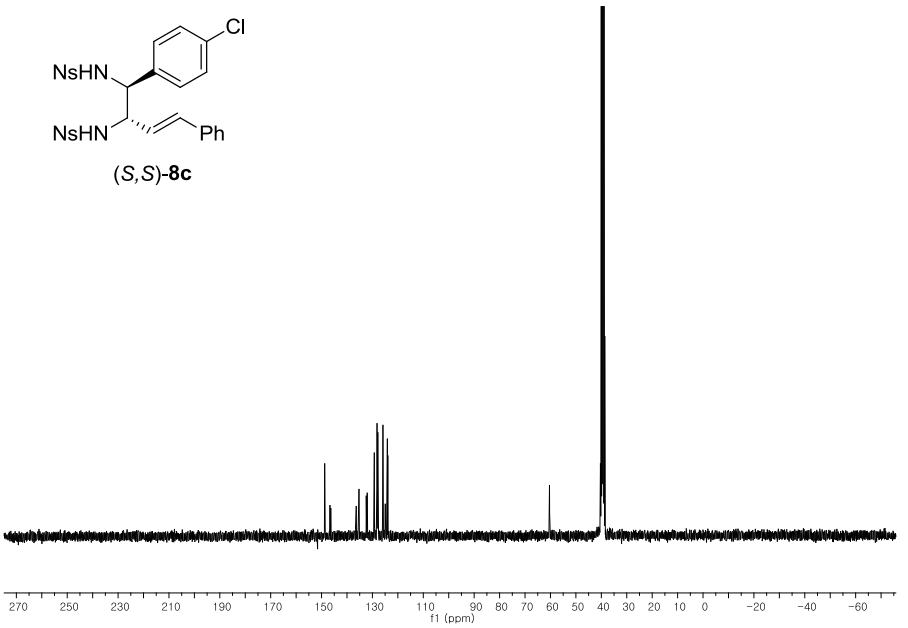


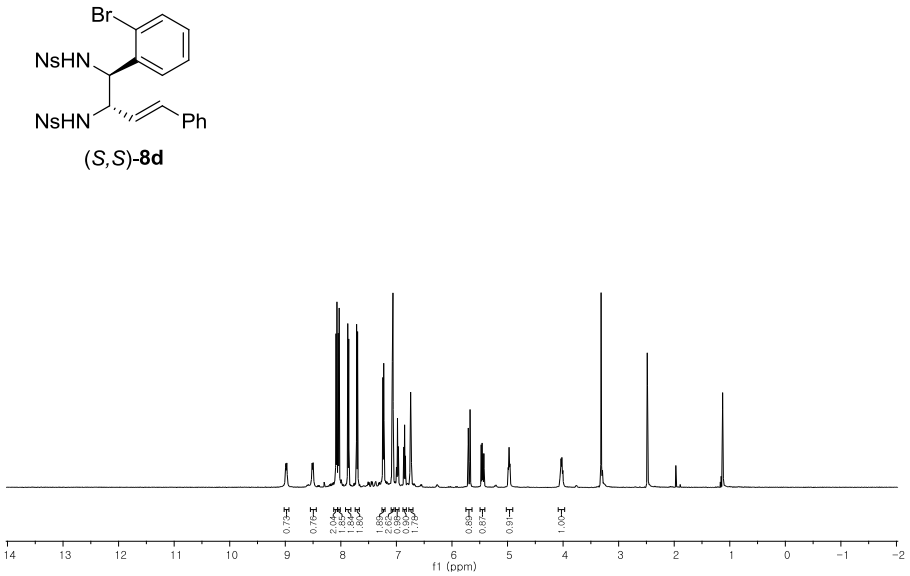
^{19}F NMR spectrum of **8b** (282 MHz, DMSO-d_6)



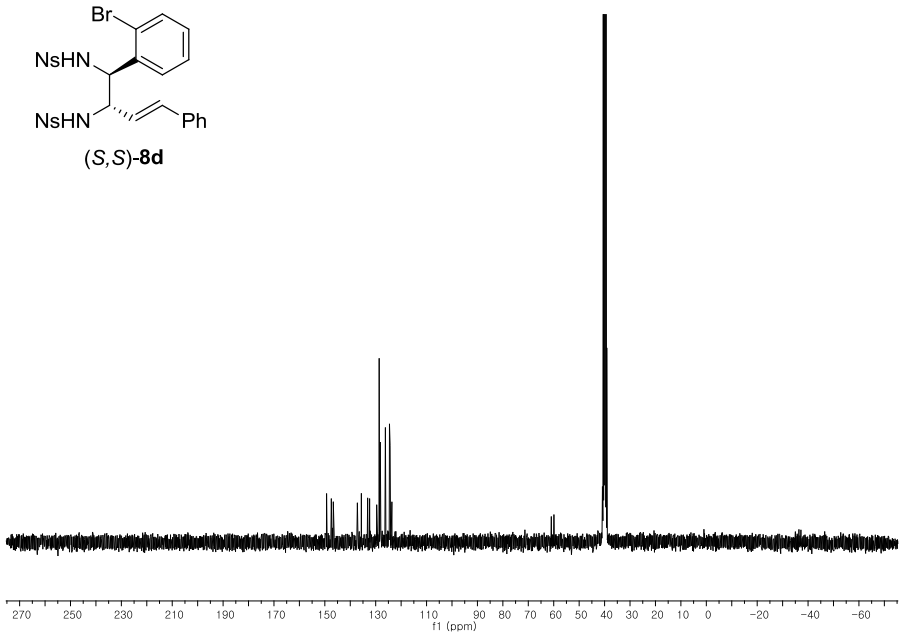
^{13}C NMR spectrum of **8c** (75 MHz, DMSO-d_6)



^{13}C NMR spectrum of **8c** (75 MHz, DMSO-d_6)



^{1}H NMR spectrum of **8d** (500 MHz, DMSO-d_6)



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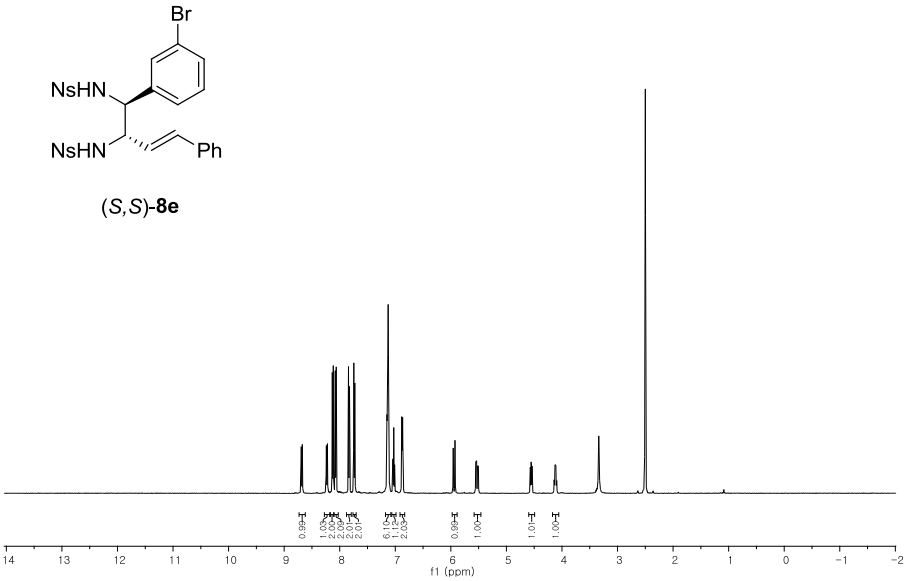

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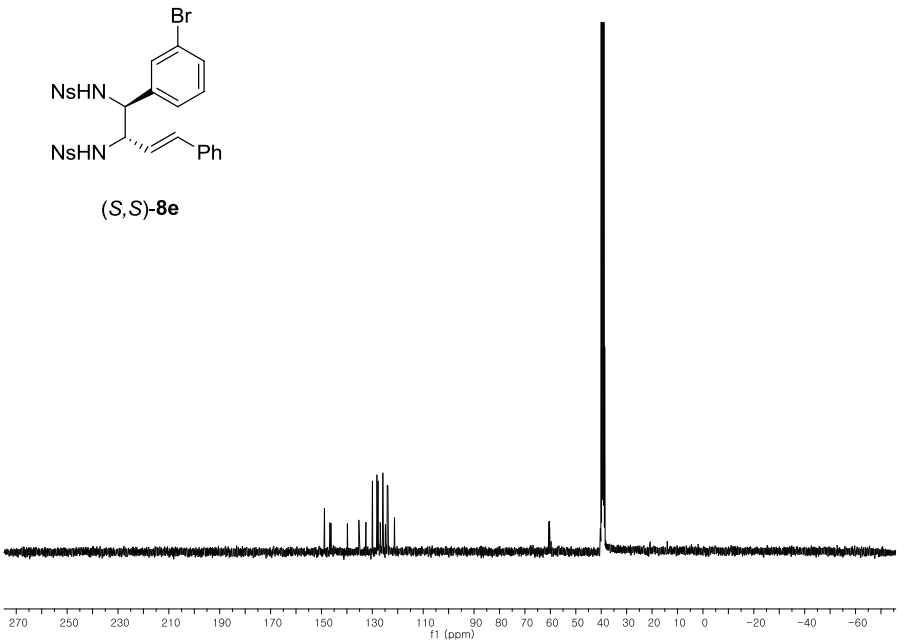

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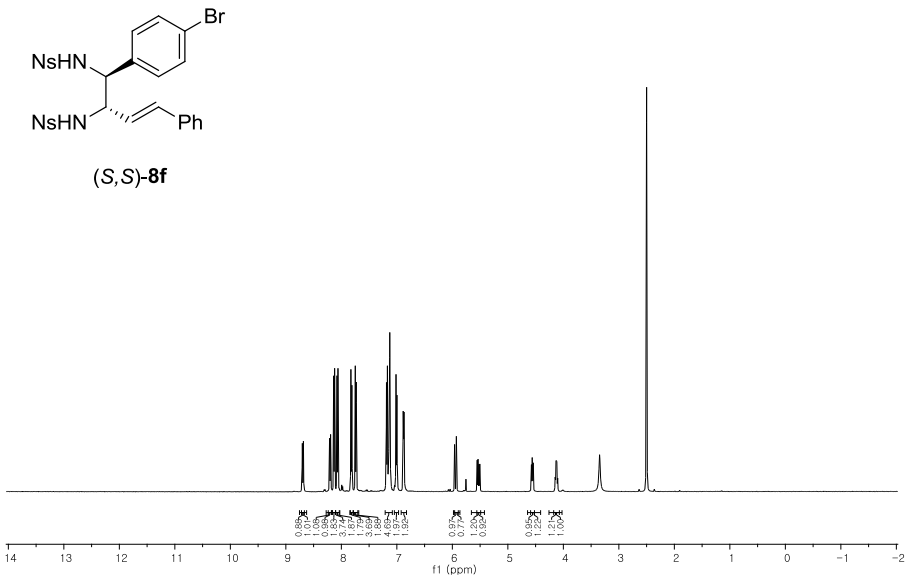

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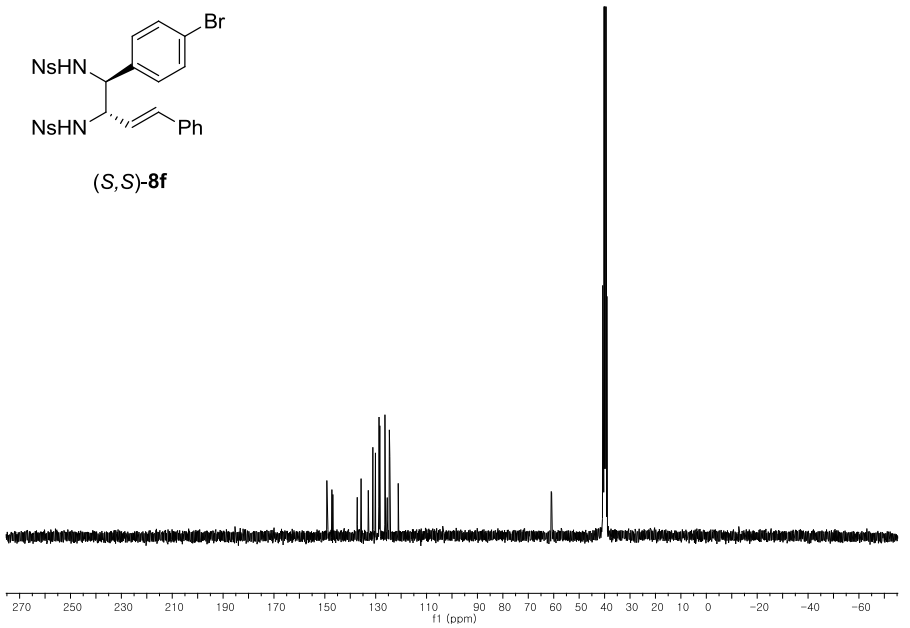

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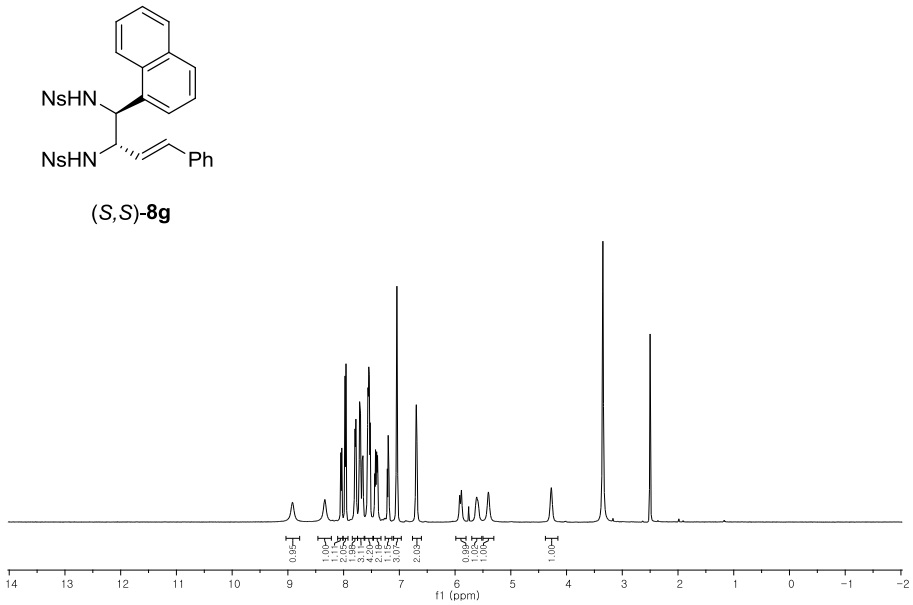

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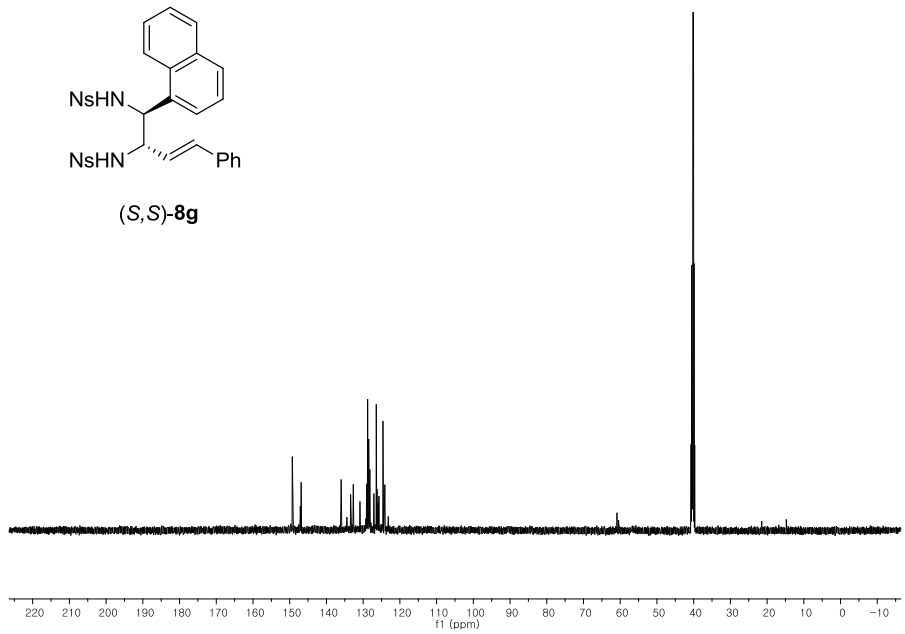

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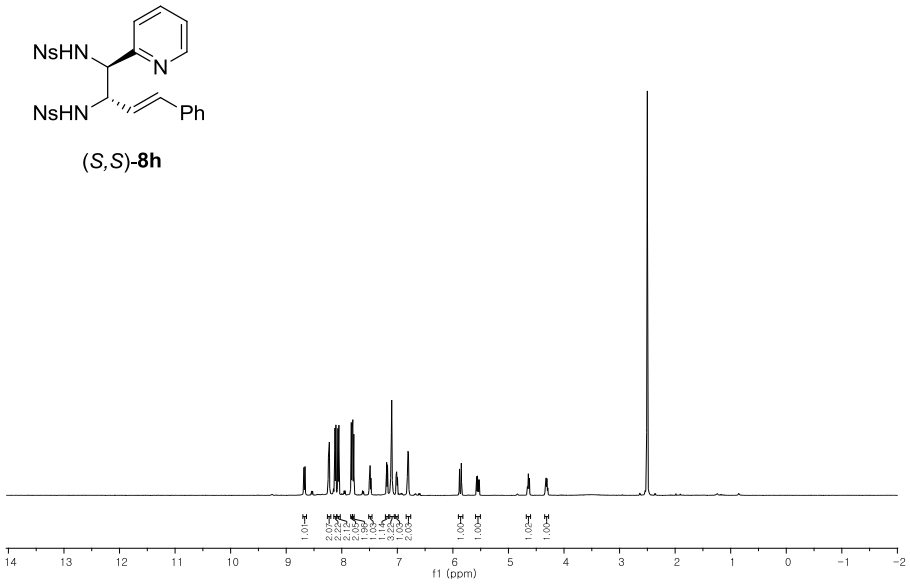

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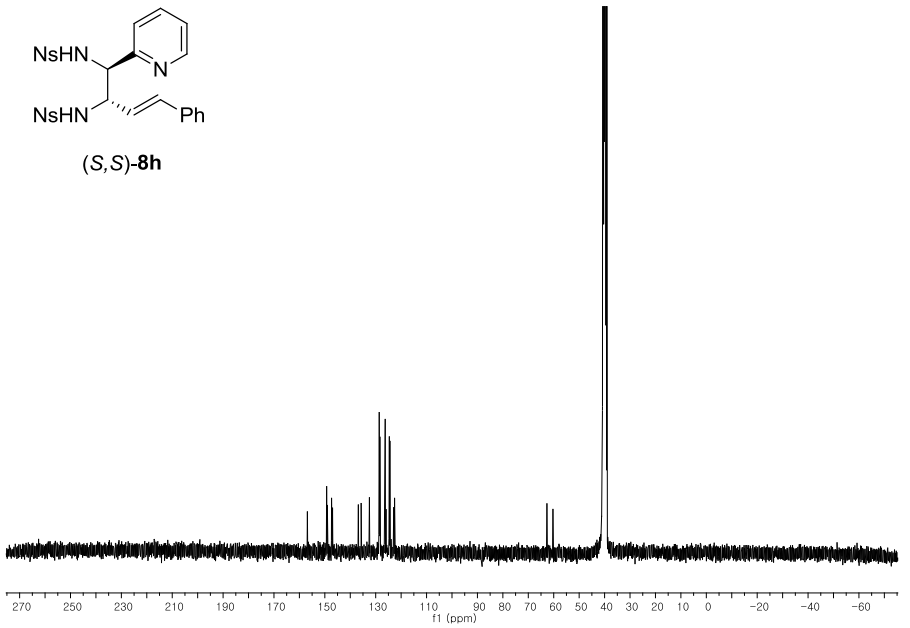

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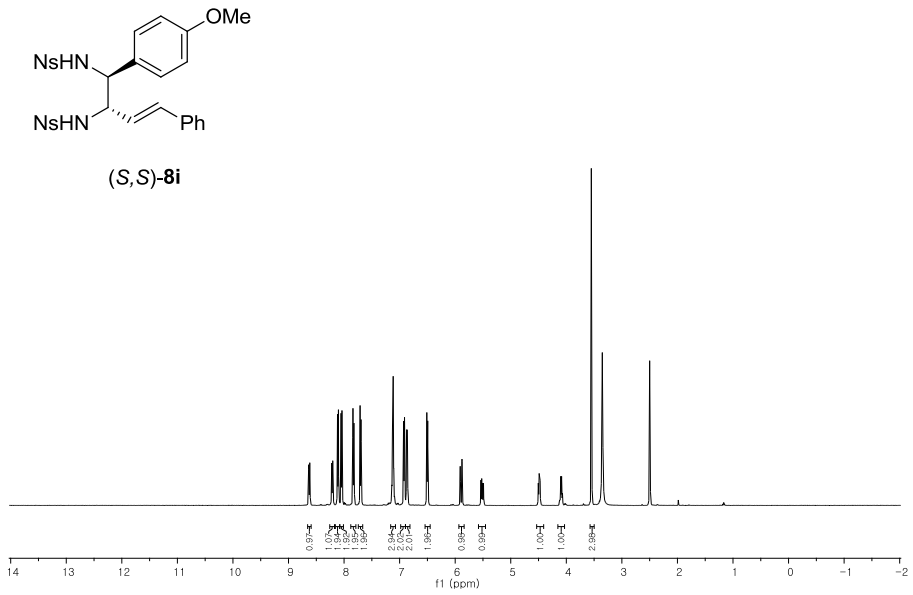

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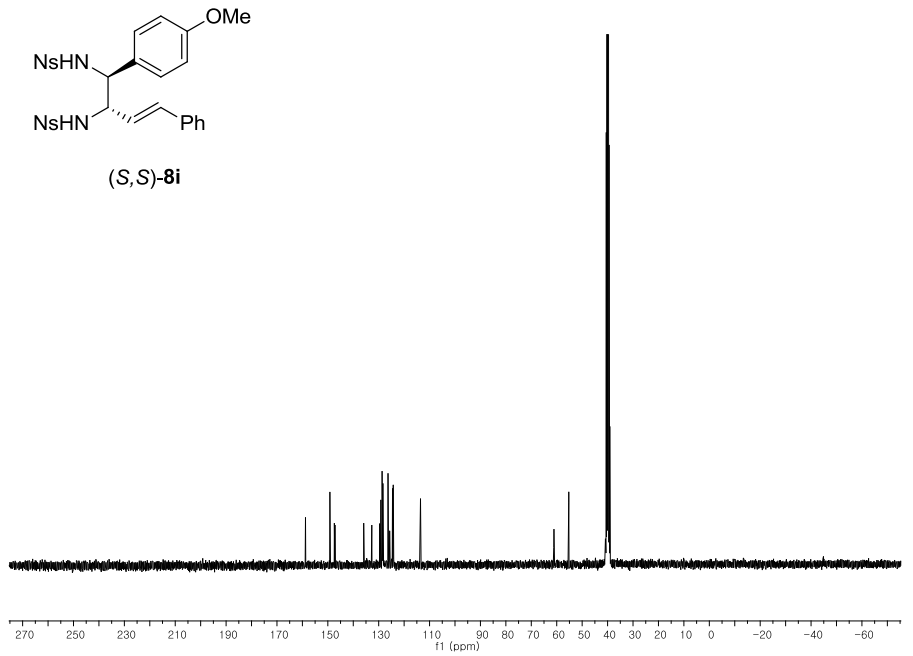

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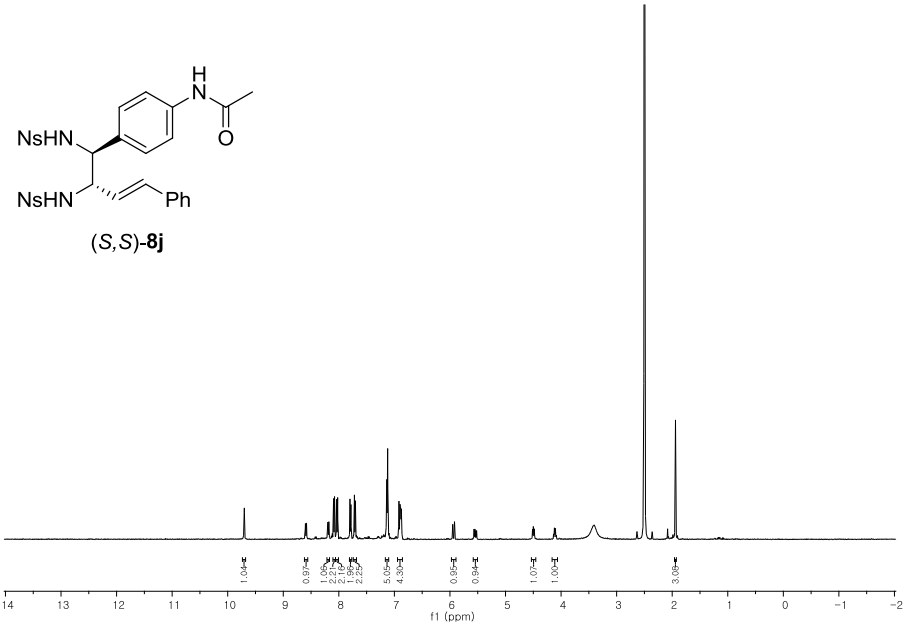

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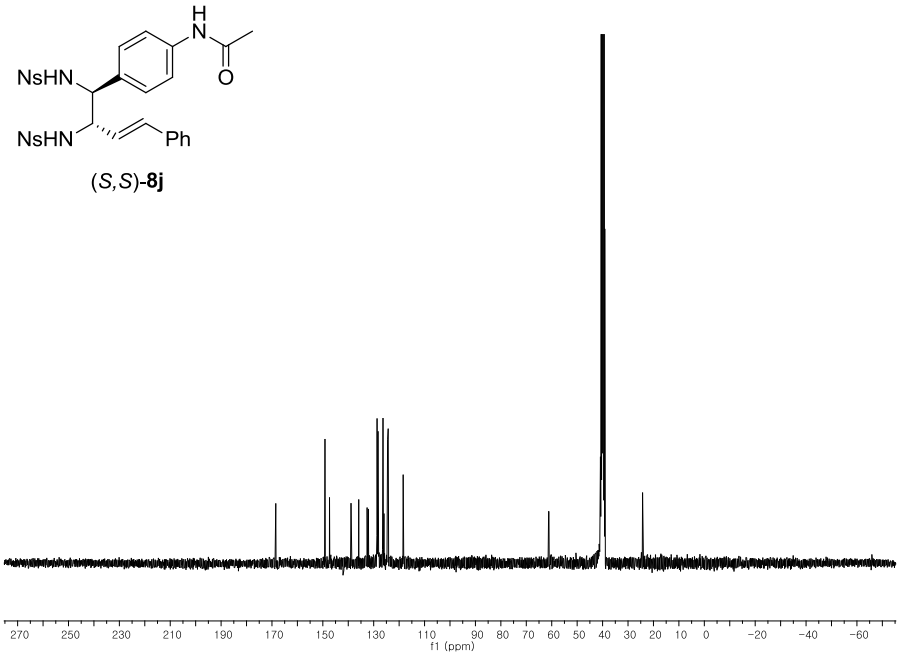

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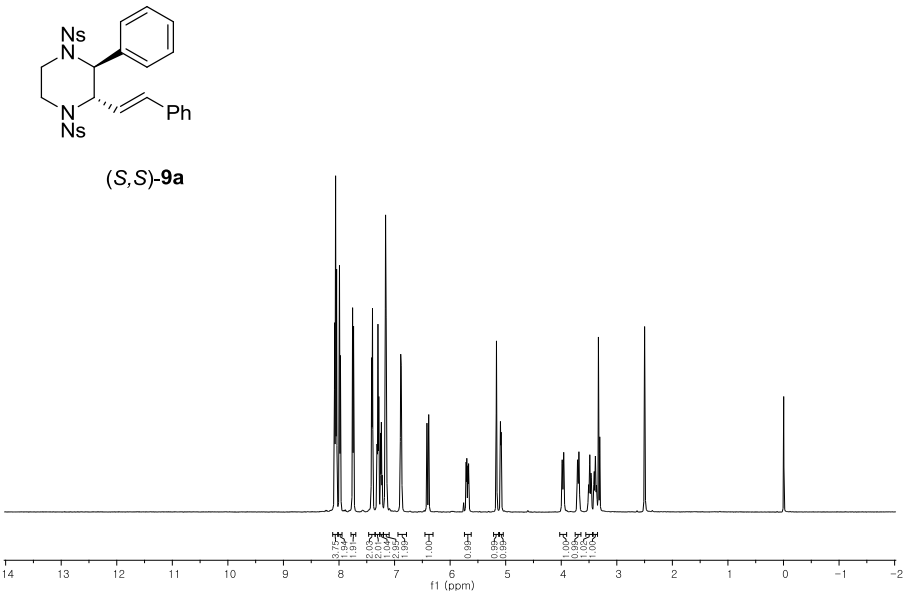

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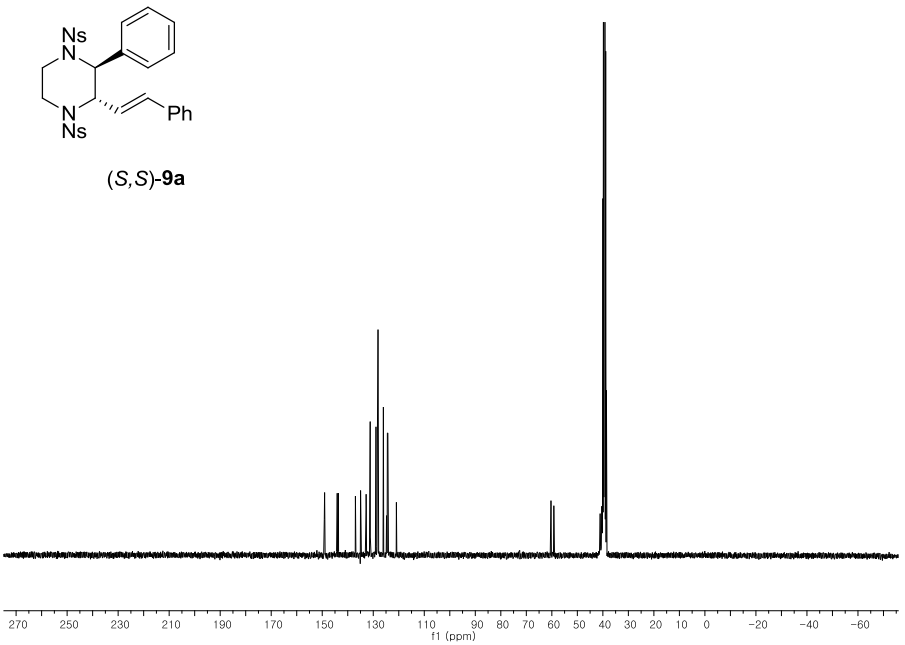

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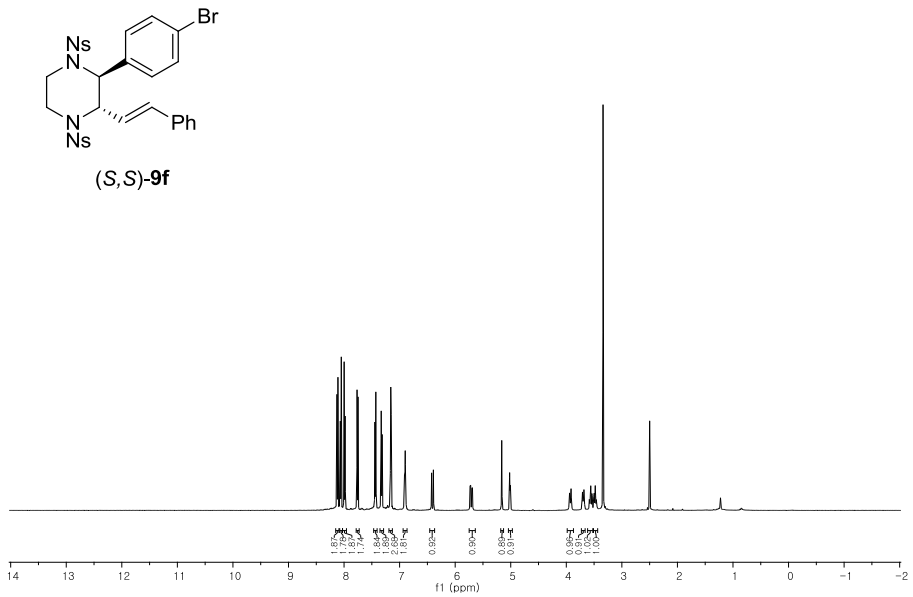
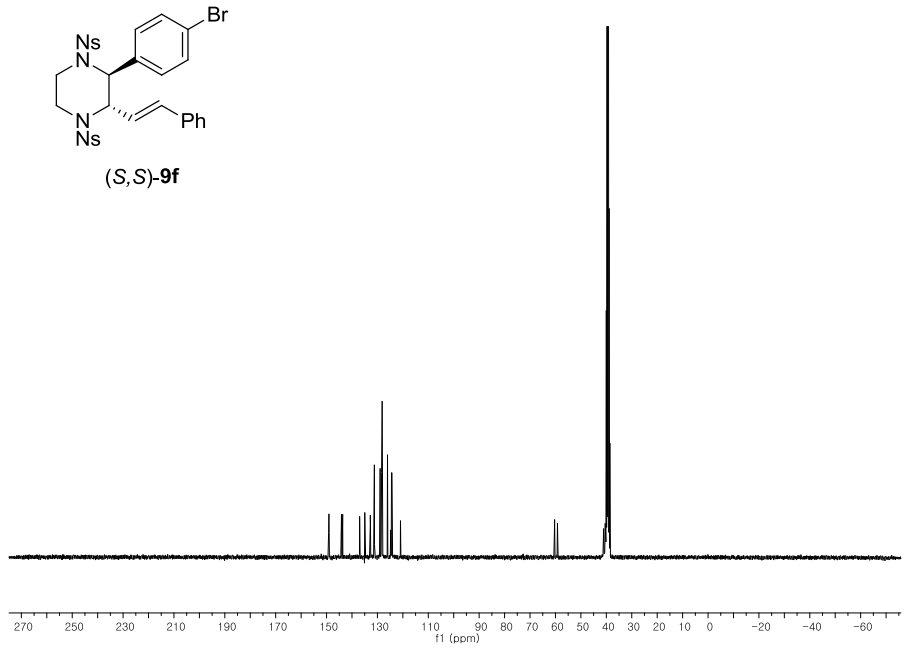


^{1}H NMR spectrum of **9f** (500 MHz, DMSO-d_6)



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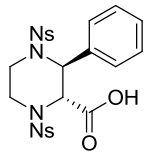

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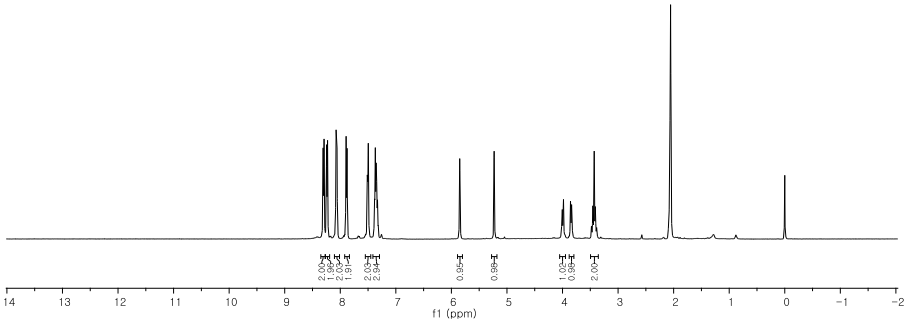

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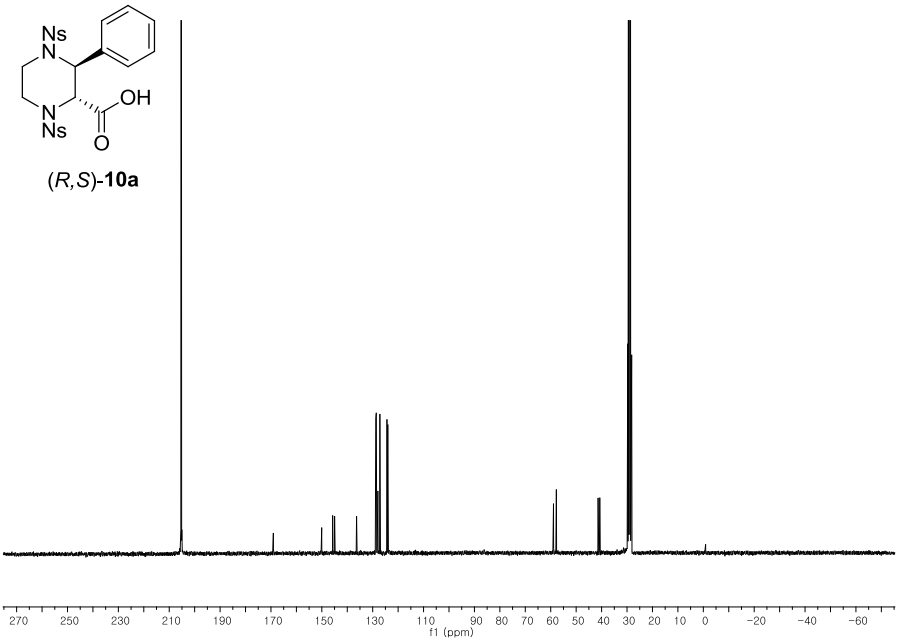
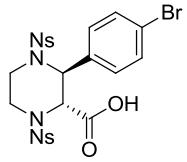
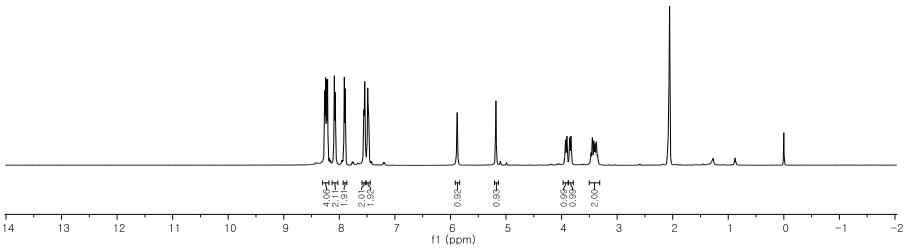


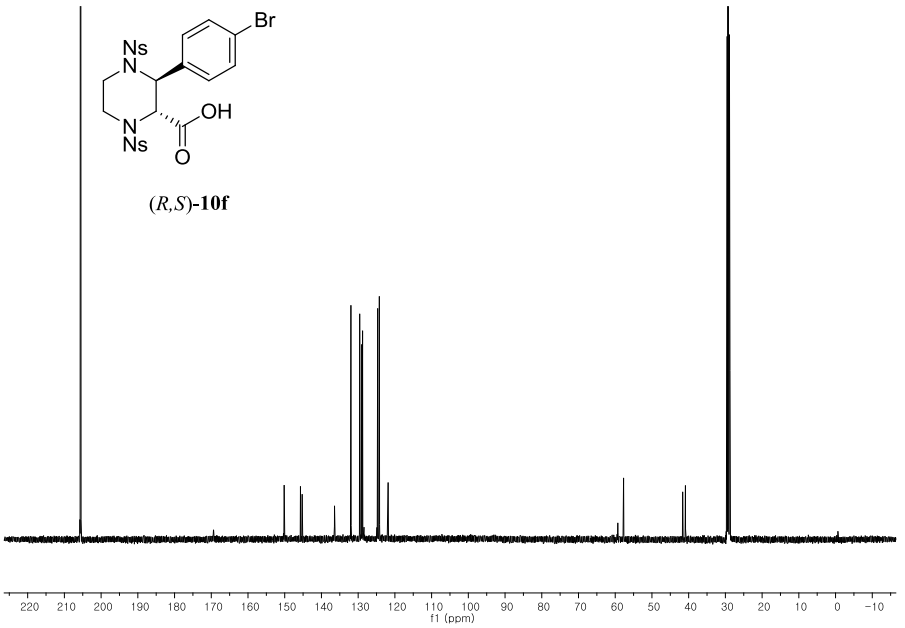
^{13}C NMR spectrum of **10a** (75 MHz, Acetone-d_6)



(*R,S*)-**10f**



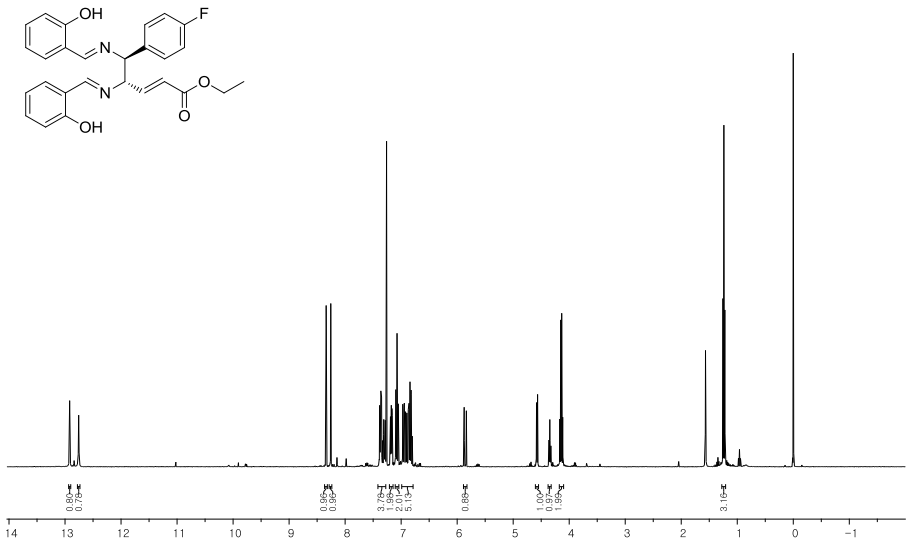
^{1}H NMR spectrum of **10f** (500 MHz, Acetone-d_6)



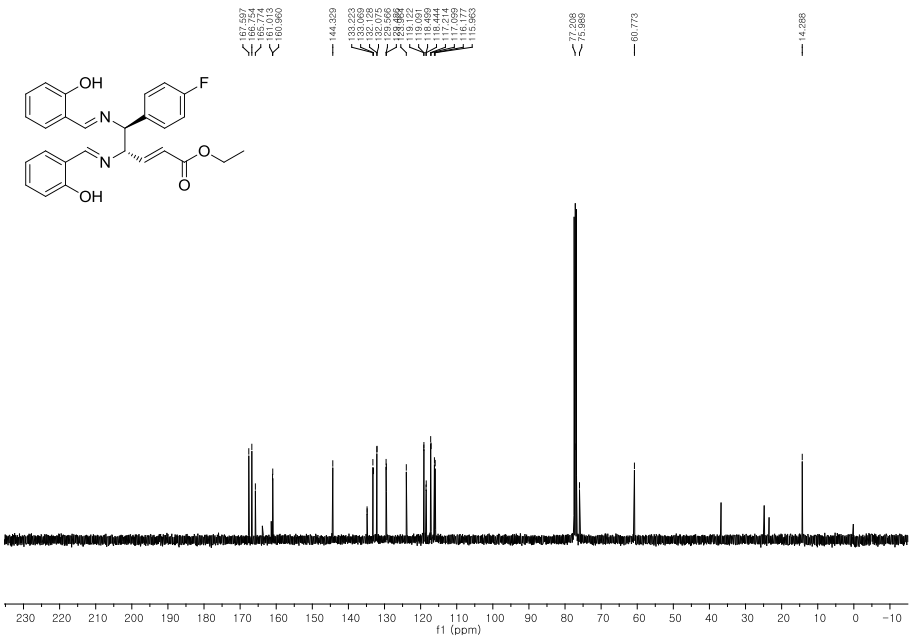
(*R,S*)-**10f**

^{13}C NMR spectrum of **10f** (126 MHz, Acetone-d_6)

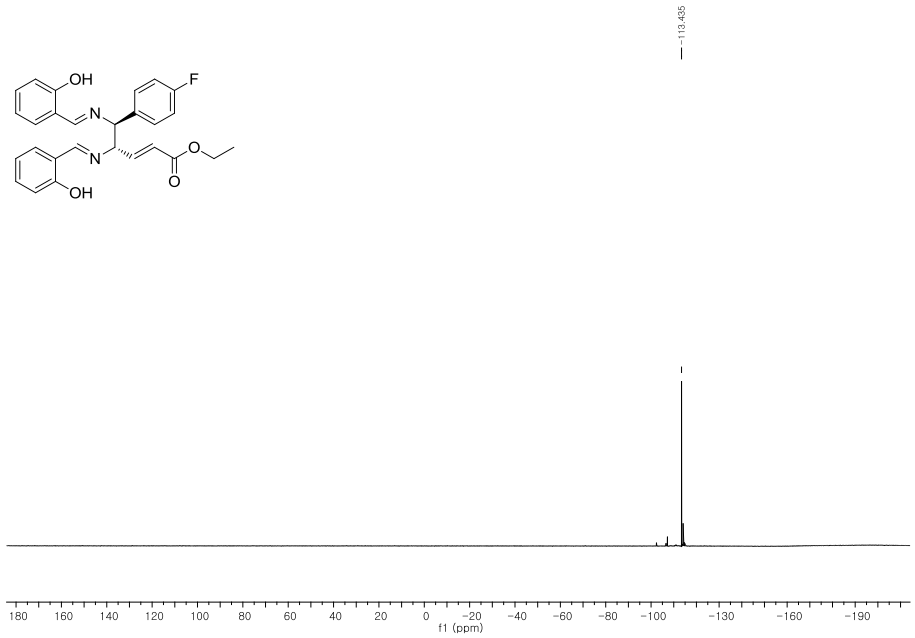
Chapter 2.



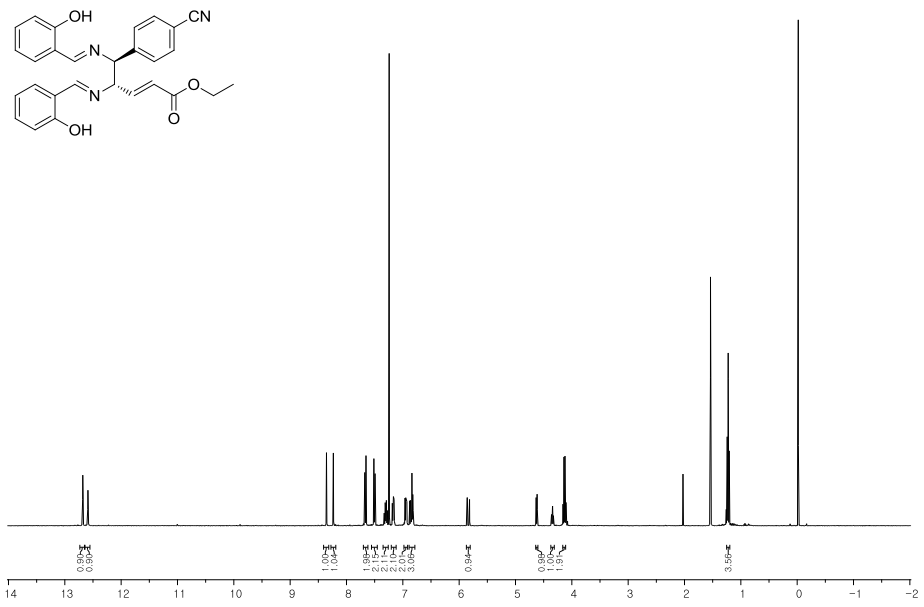
^{1}H NMR spectrum of **3a** (400 MHz, $CDCl_3$)



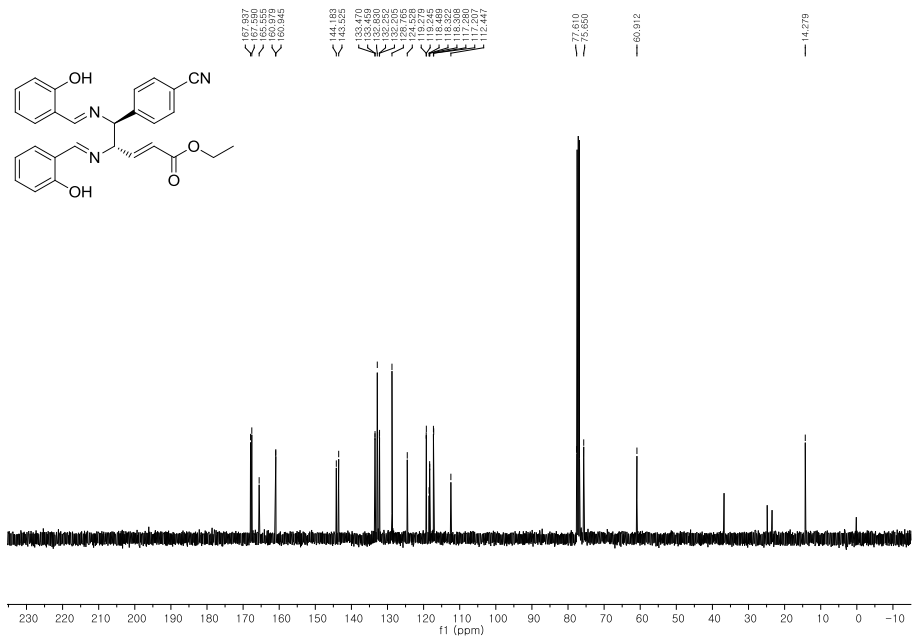
^{13}C NMR spectrum of **3a** (100 MHz, $CDCl_3$)



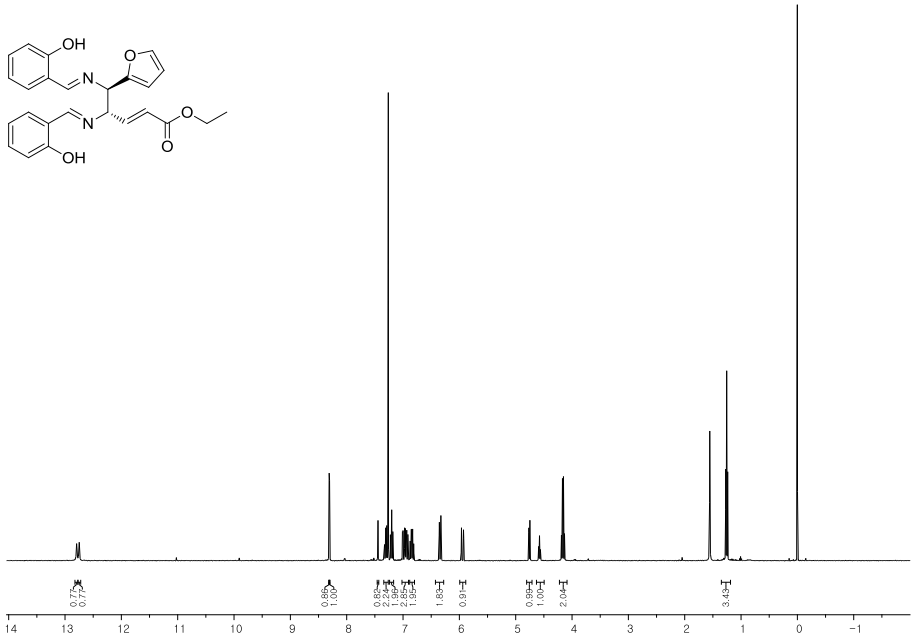
Proton-decoupled ^{19}F NMR spectrum of **3a** (377 MHz, $CDCl_3$)



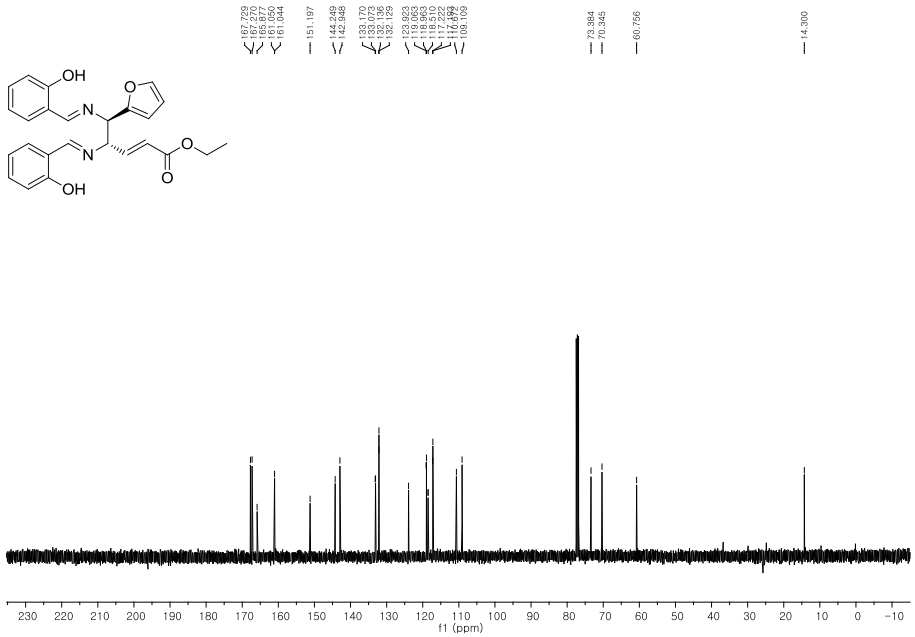
^{1}H NMR spectrum of **3b** (400 MHz, $CDCl_3$)



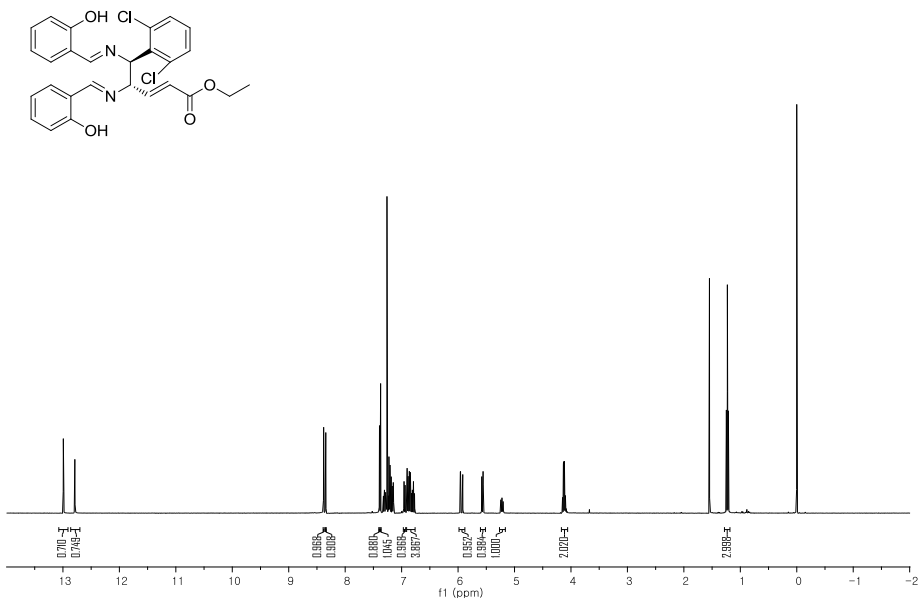
^{13}C NMR spectrum of **3b** (100 MHz, $CDCl_3$)



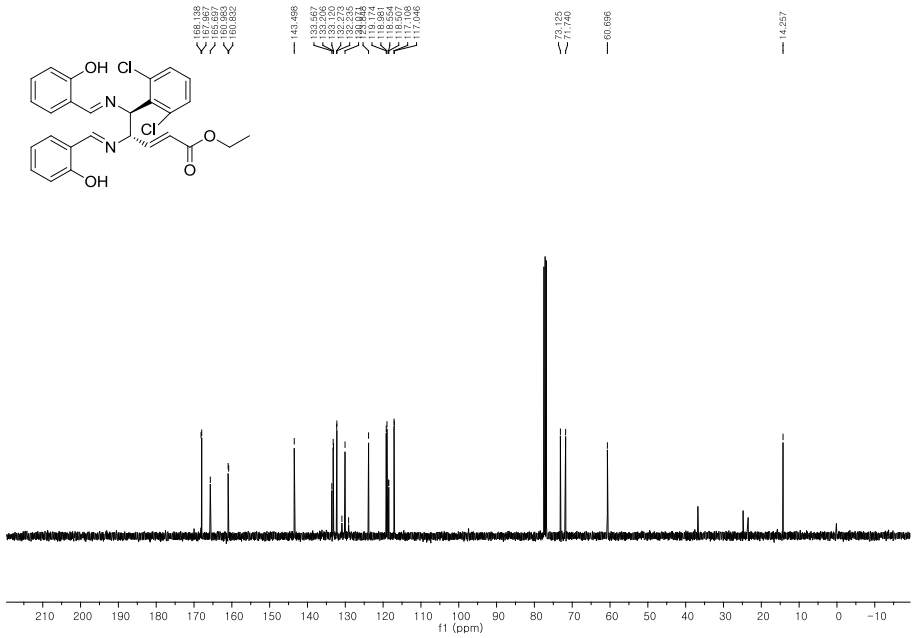
^{1}H NMR spectrum of **3c** (400 MHz, $CDCl_3$)



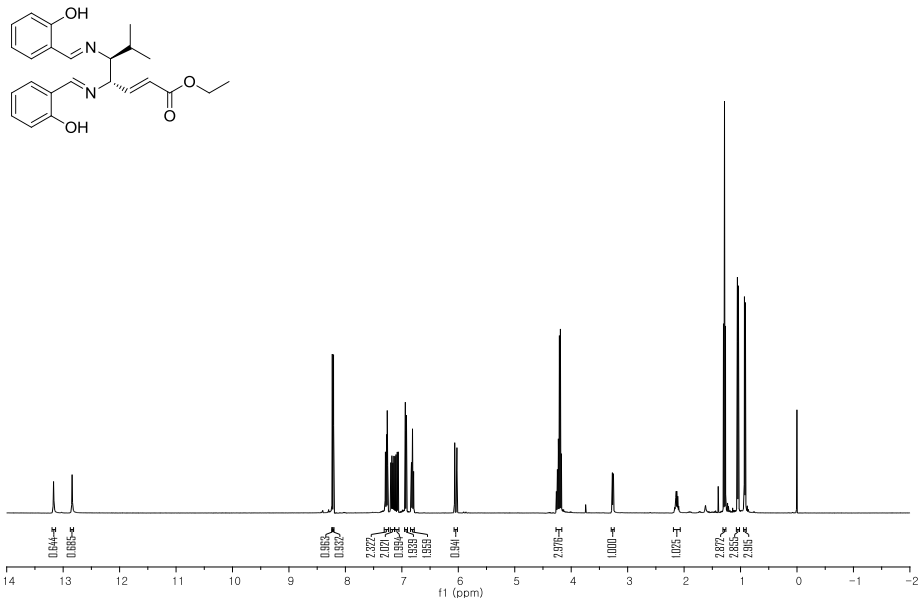
^{13}C NMR spectrum of **3c** (100 MHz, $CDCl_3$)



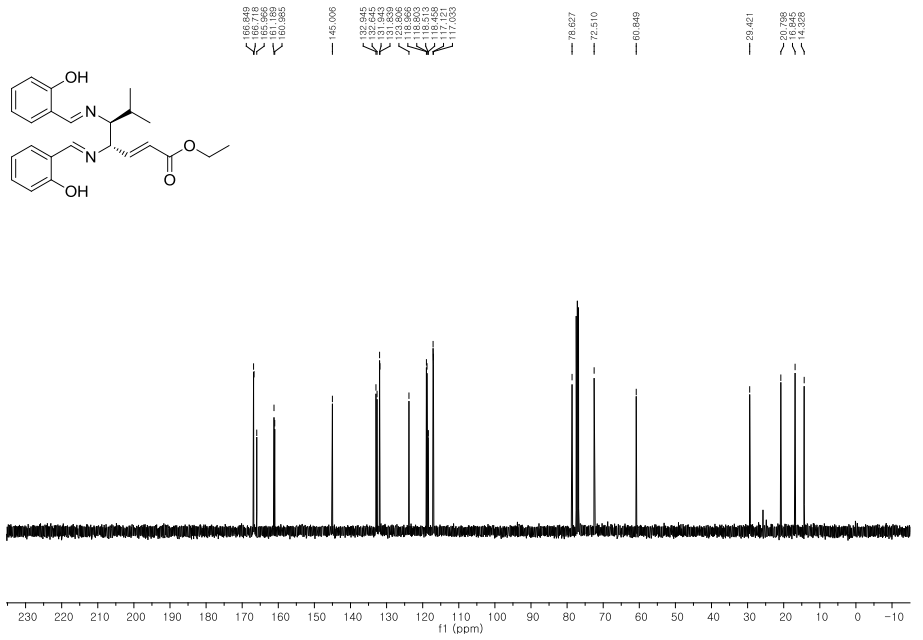
^{1}H NMR spectrum of **3d** (400 MHz, $CDCl_3$)



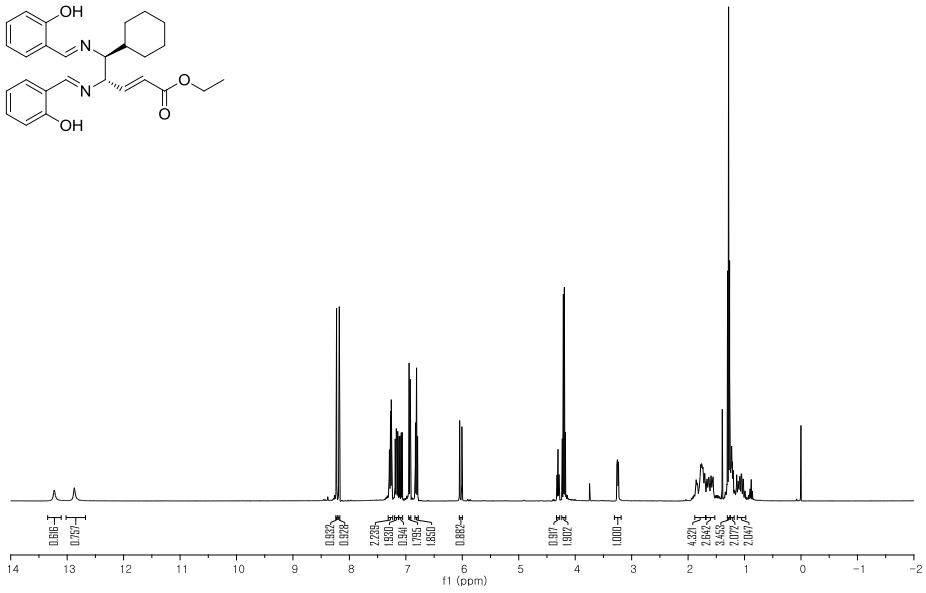
^{13}C NMR spectrum of **3d** (100 MHz, $CDCl_3$)



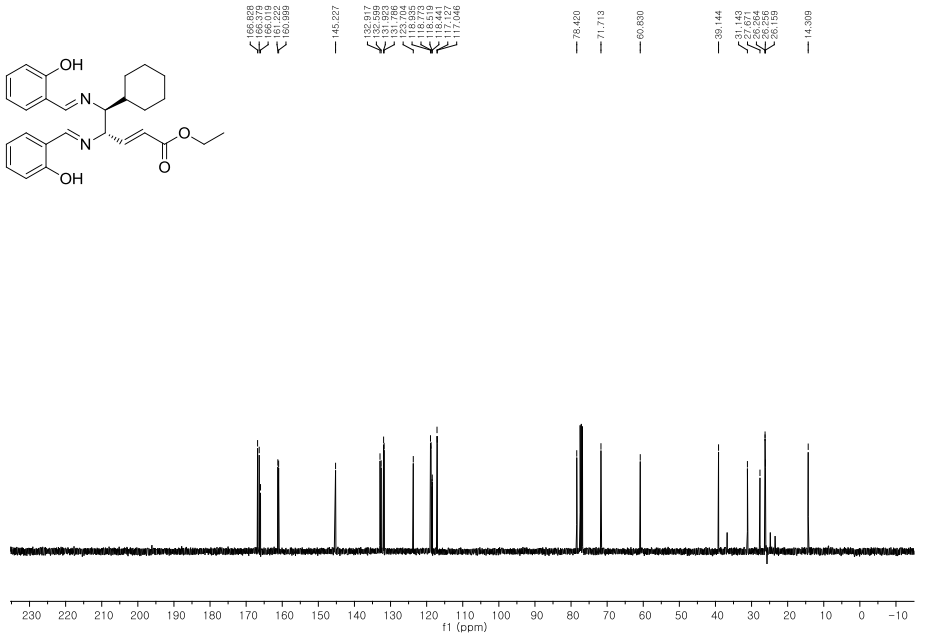
^{1}H NMR spectrum of **3e** (400 MHz, $CDCl_3$)



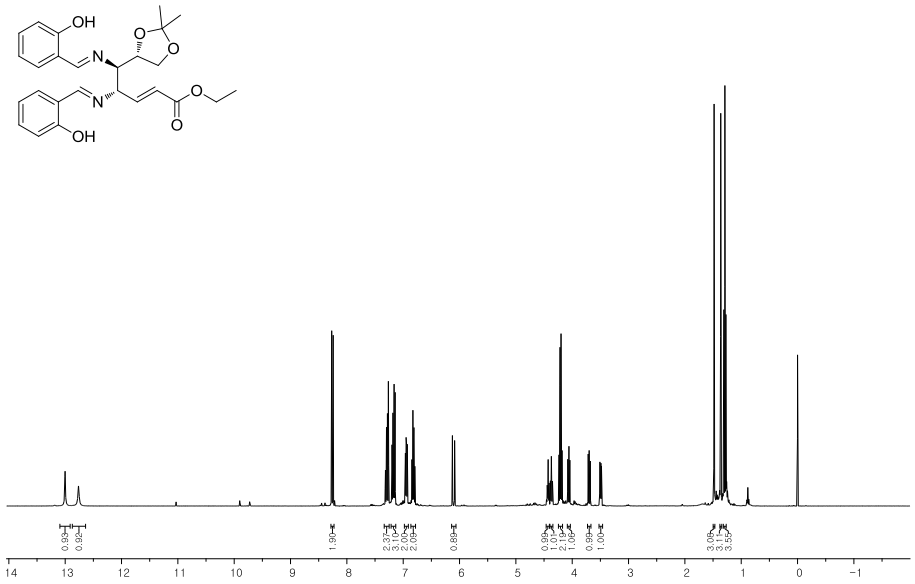
^{13}C NMR spectrum of **3e** (100 MHz, $CDCl_3$)



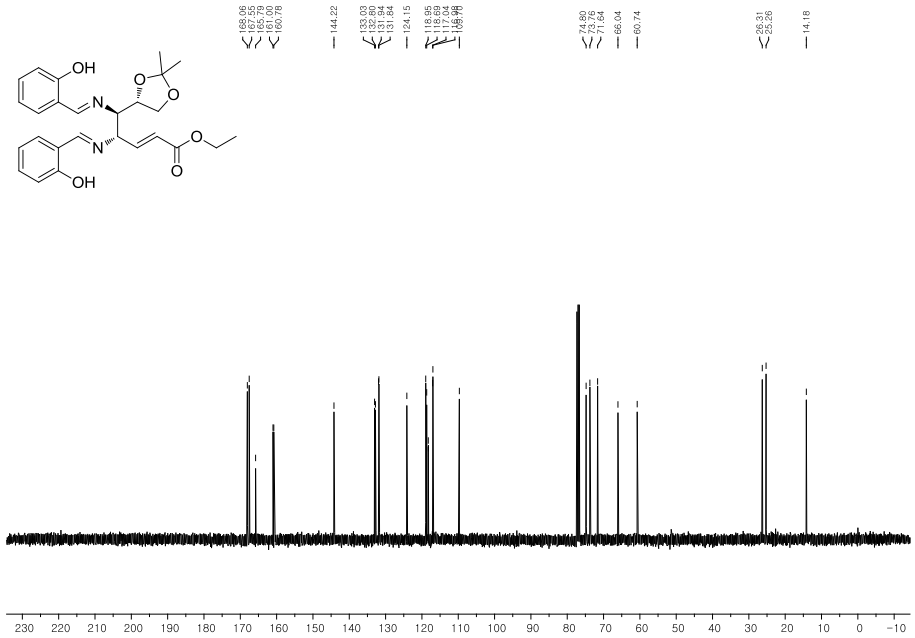
^{1}H NMR spectrum of **3f** (400 MHz, $CDCl_3$)



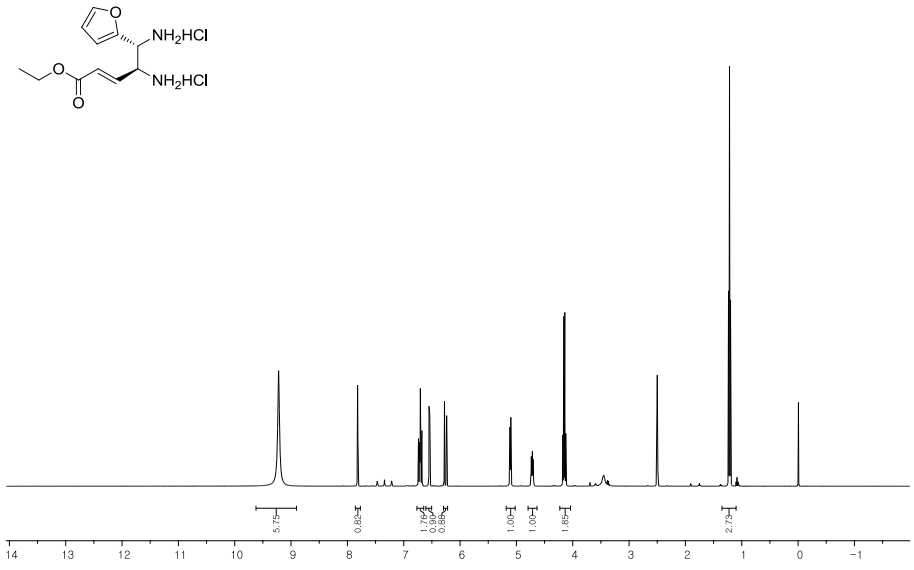
^{13}C NMR spectrum of **3f** (100 MHz, $CDCl_3$)



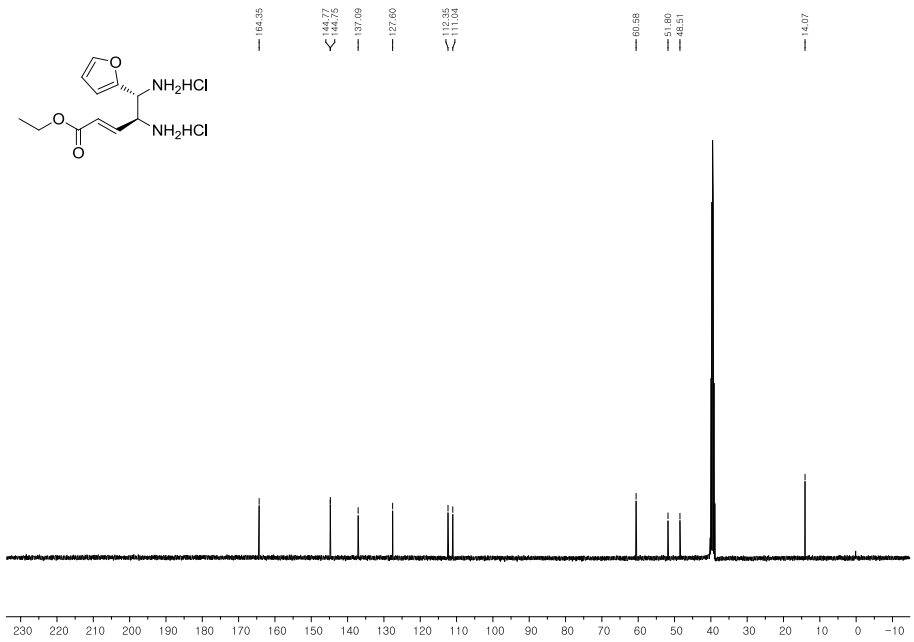
^{1}H NMR spectrum of **3g** (400 MHz, $CDCl_3$)



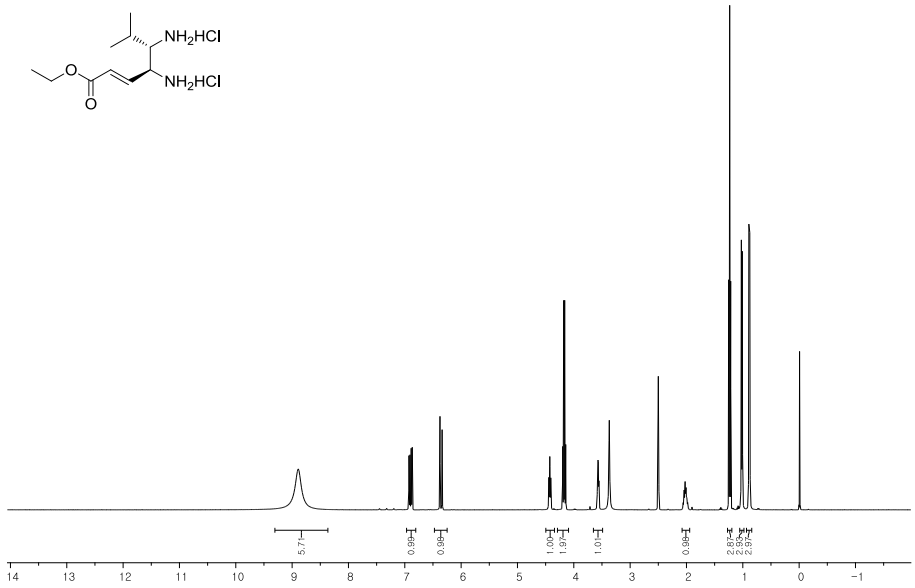
^{13}C NMR spectrum of **3g** (100 MHz, $CDCl_3$)



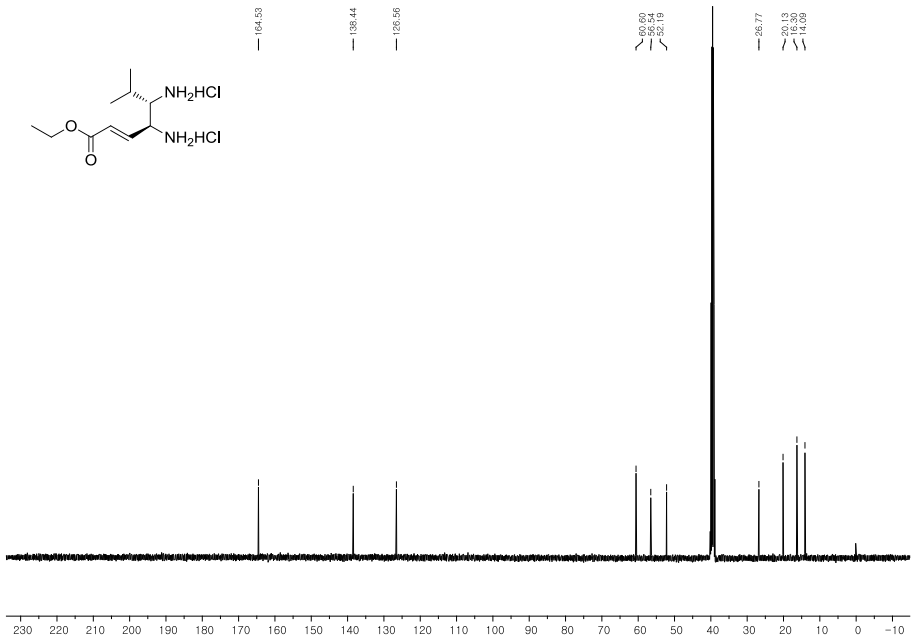
^{1}H NMR spectrum of **7c** (400 MHz, DMSO-d_6)



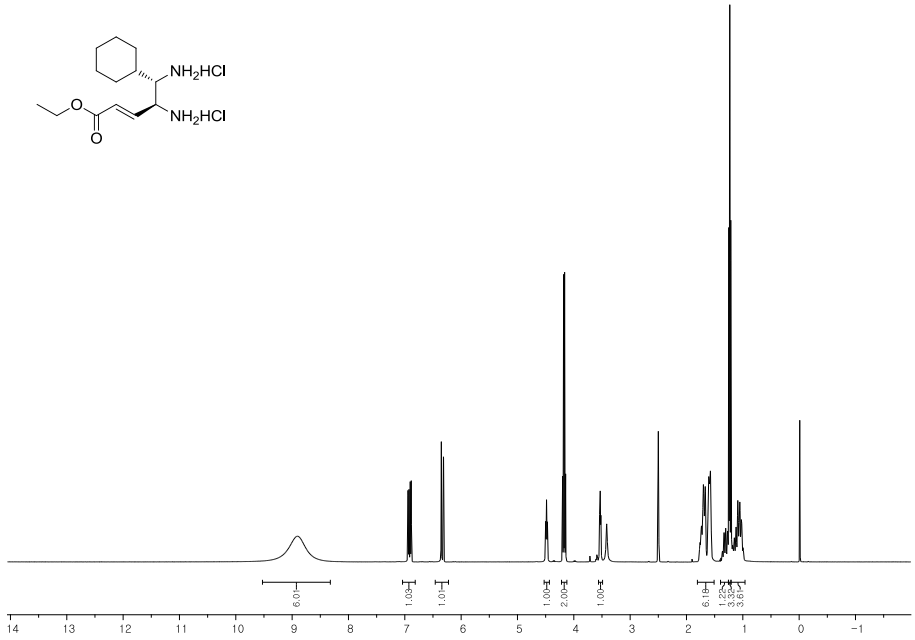
^{13}C NMR spectrum of **7c** (100 MHz, DMSO-d_6)



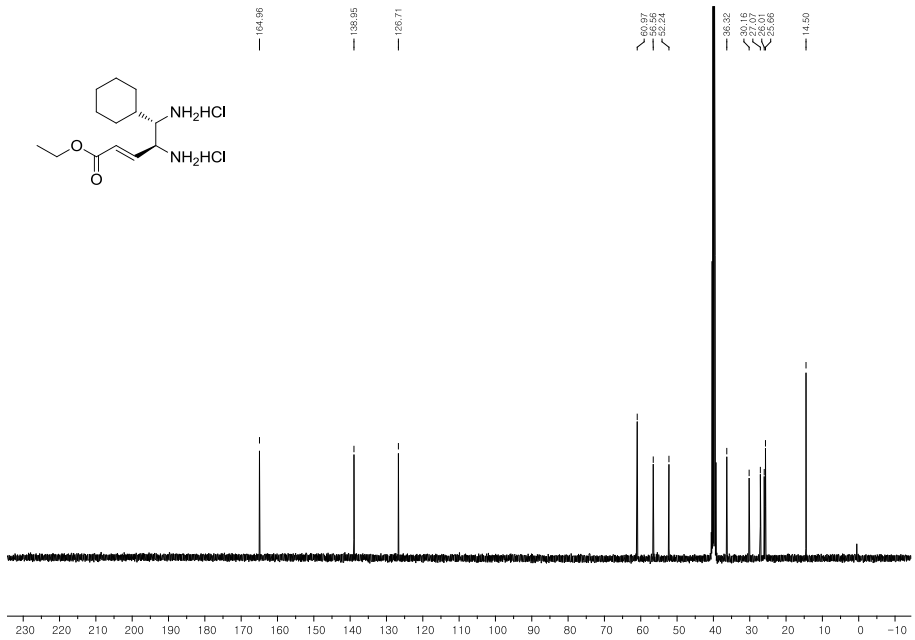
^{1}H NMR spectrum of **7e** (400 MHz, DMSO-d_6)



^{13}C NMR spectrum of **7e** (100 MHz, DMSO-d_6)

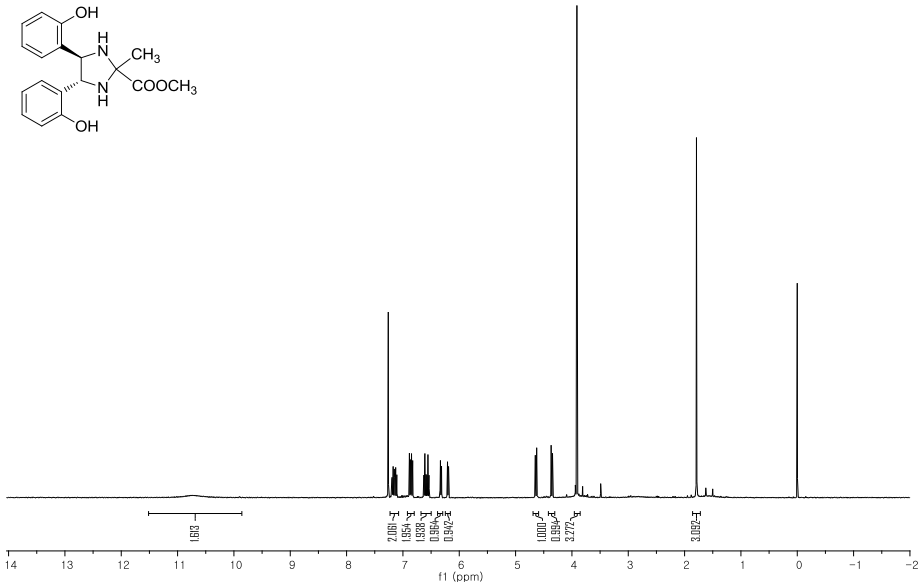


^{1}H NMR spectrum of **7f** (400 MHz, DMSO-d_6)

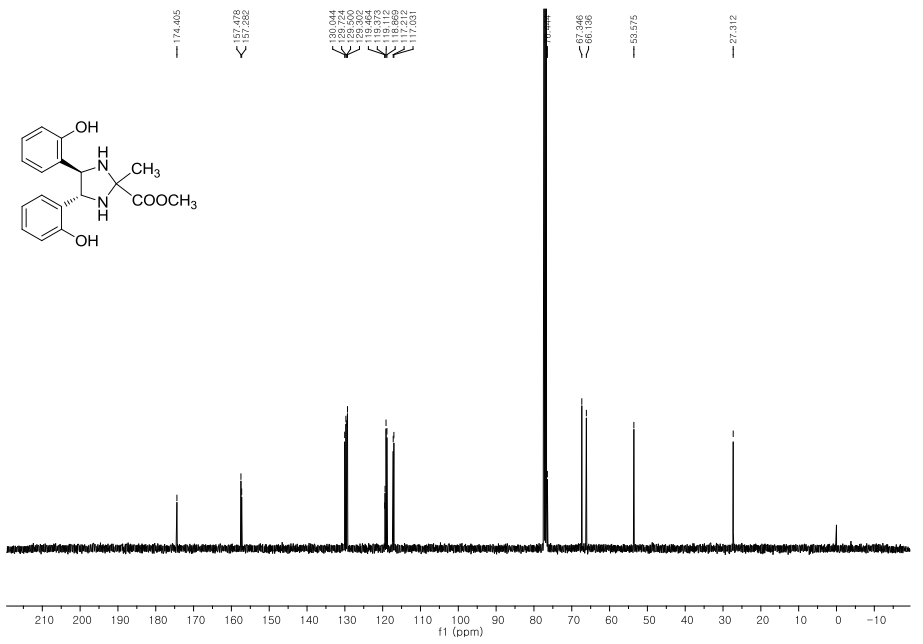


^{13}C NMR spectrum of **7f** (100 MHz, DMSO-d_6)

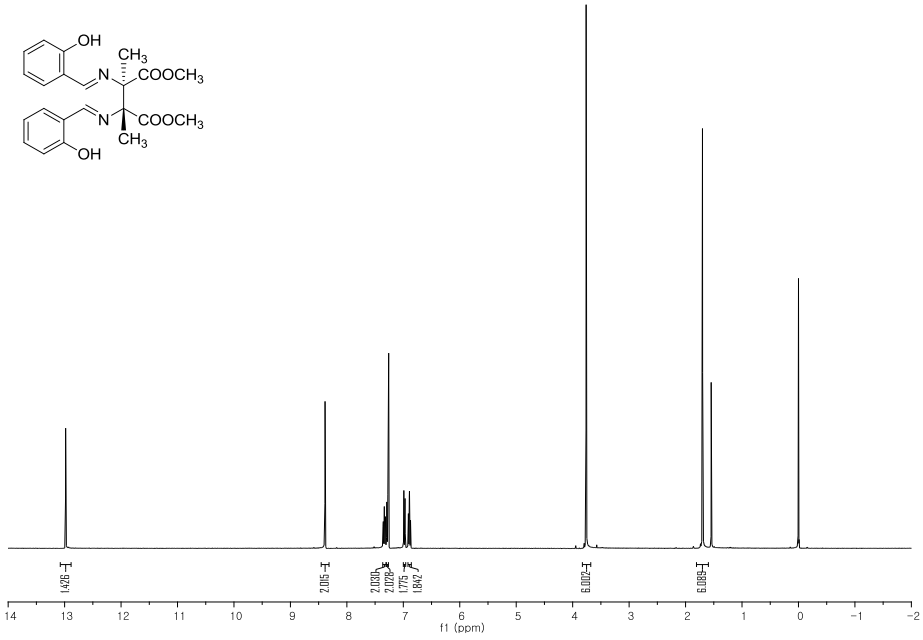
Chapter 3.



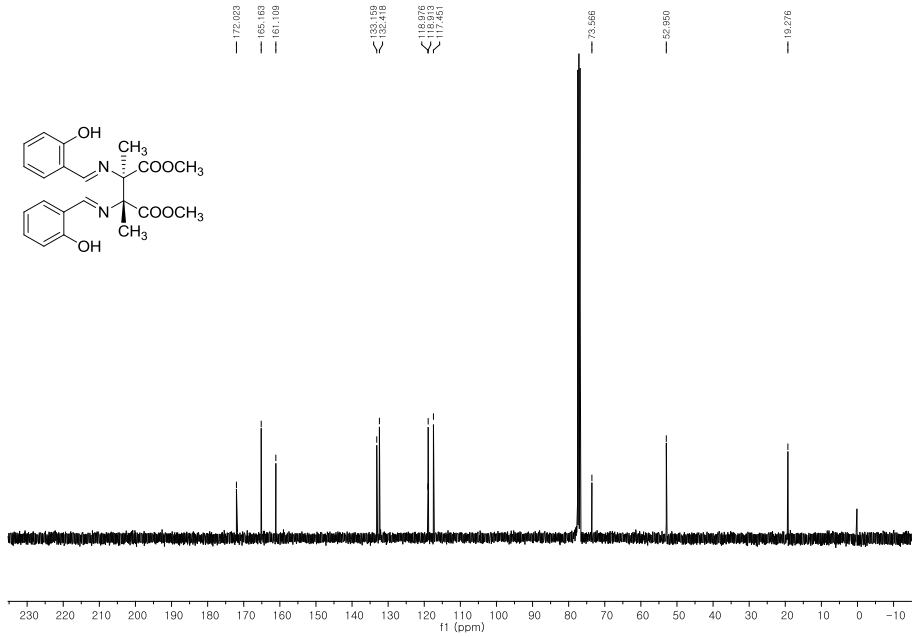
^{1}H NMR spectrum of **1** (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of **1** (101 MHz, $CDCl_3$)

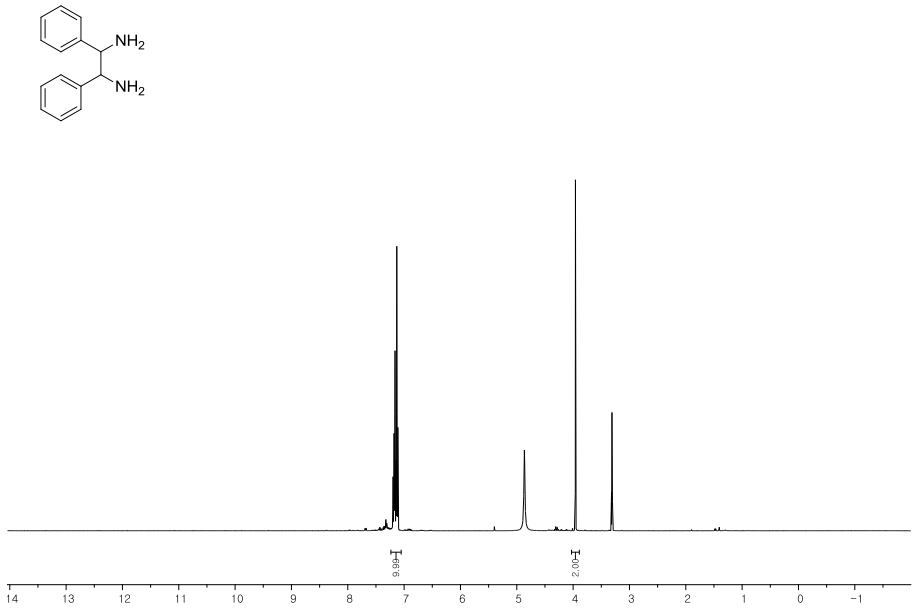


^{1}H NMR spectrum of **3** (400 MHz, $CDCl_3$)

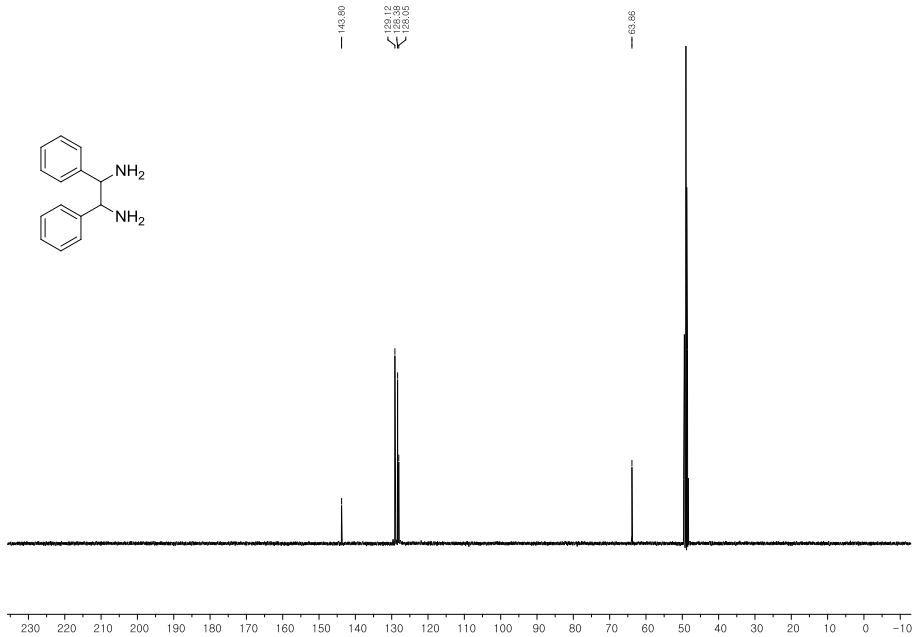


^{13}C NMR spectrum of **3** (101 MHz, $CDCl_3$)

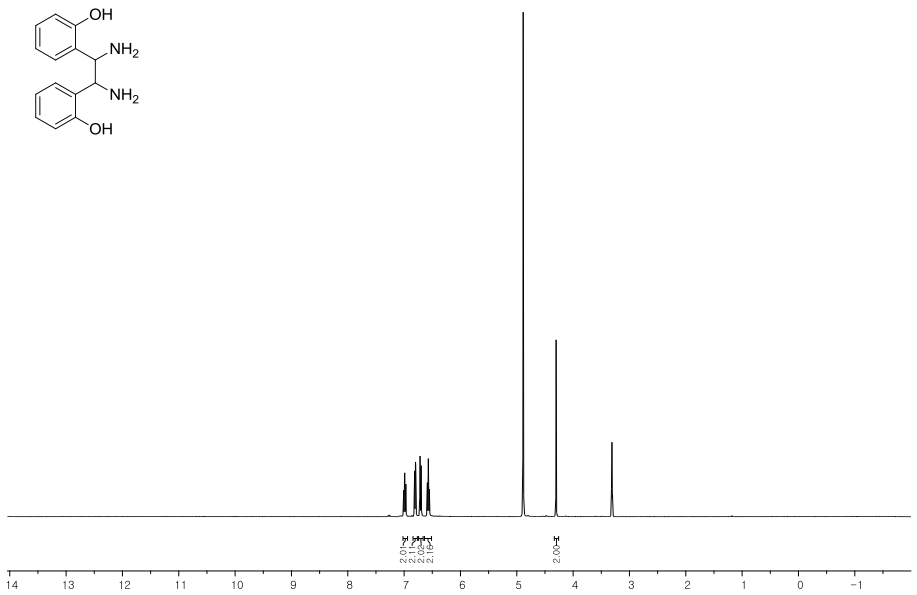
Chapter 4.



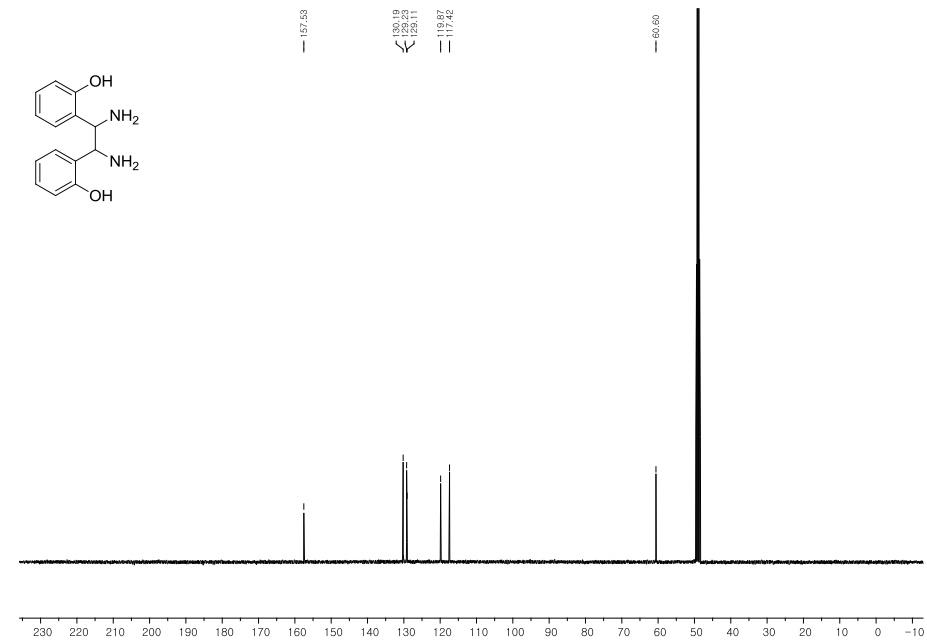
^{1}H NMR spectrum of **1** (400 MHz, MeOD-d_3)



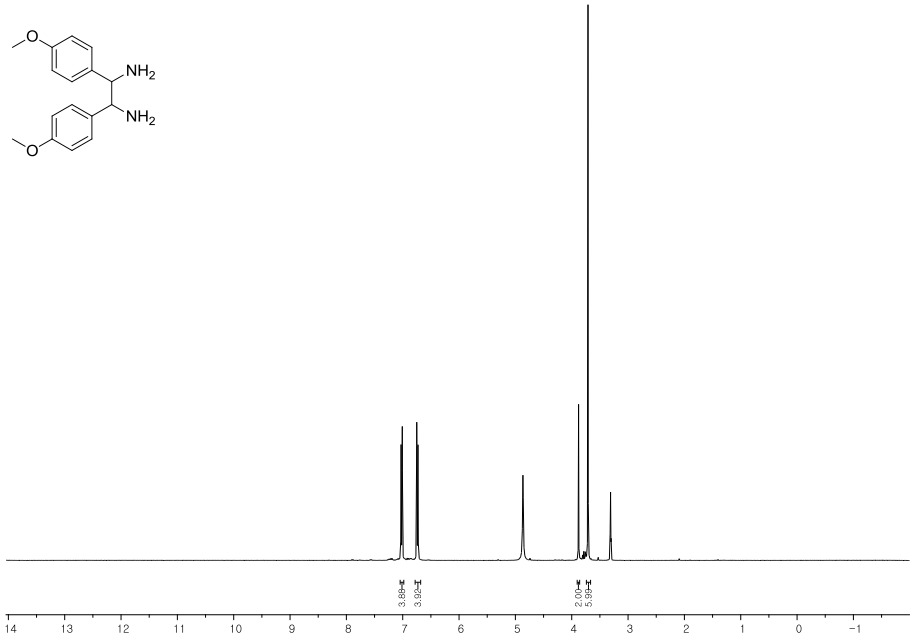
^{13}C NMR spectrum of **1** (101 MHz, MeOD-d_3)



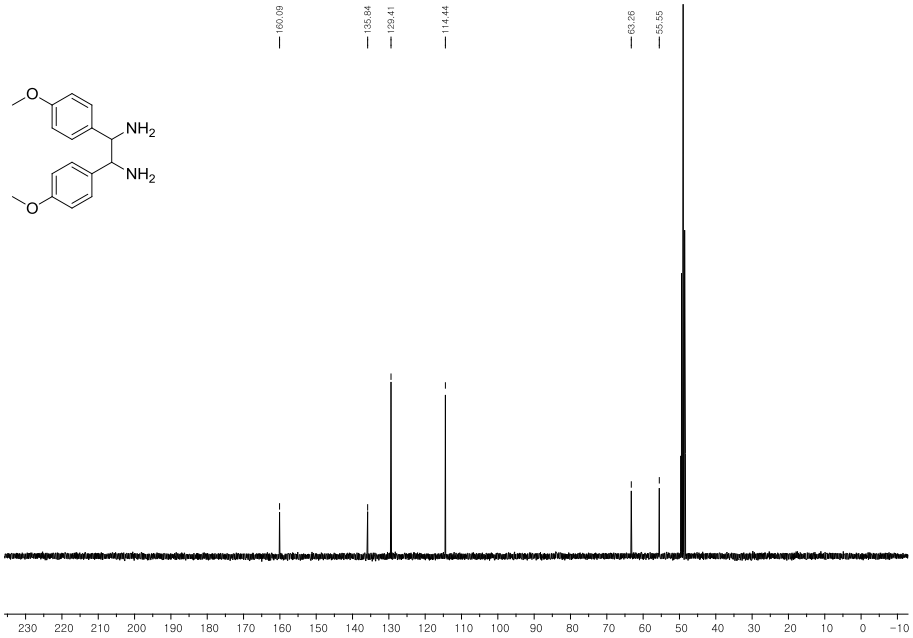
^{1}H NMR spectrum of **2** (400 MHz, MeOD-d_3)



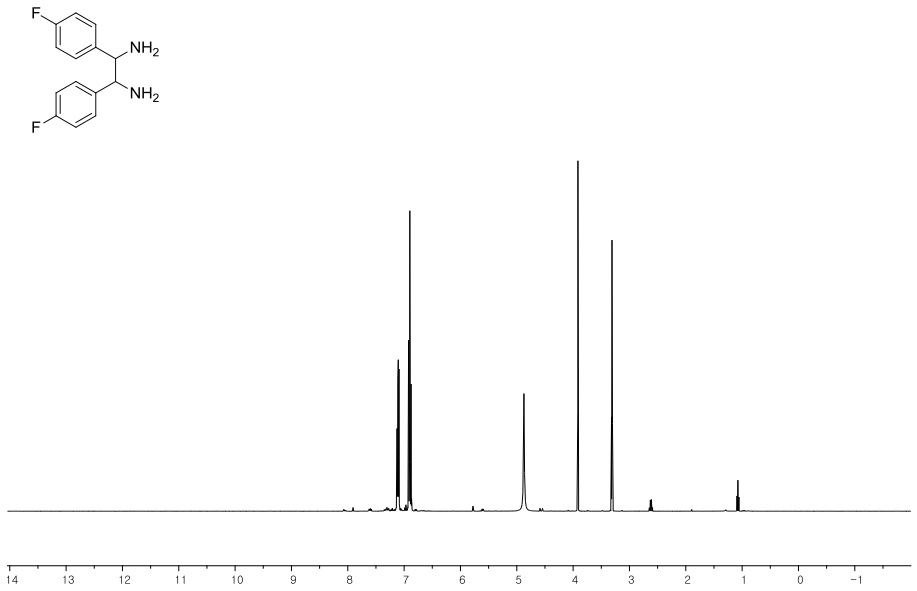
^{13}C NMR spectrum of **2** (101 MHz, MeOD-d_3)



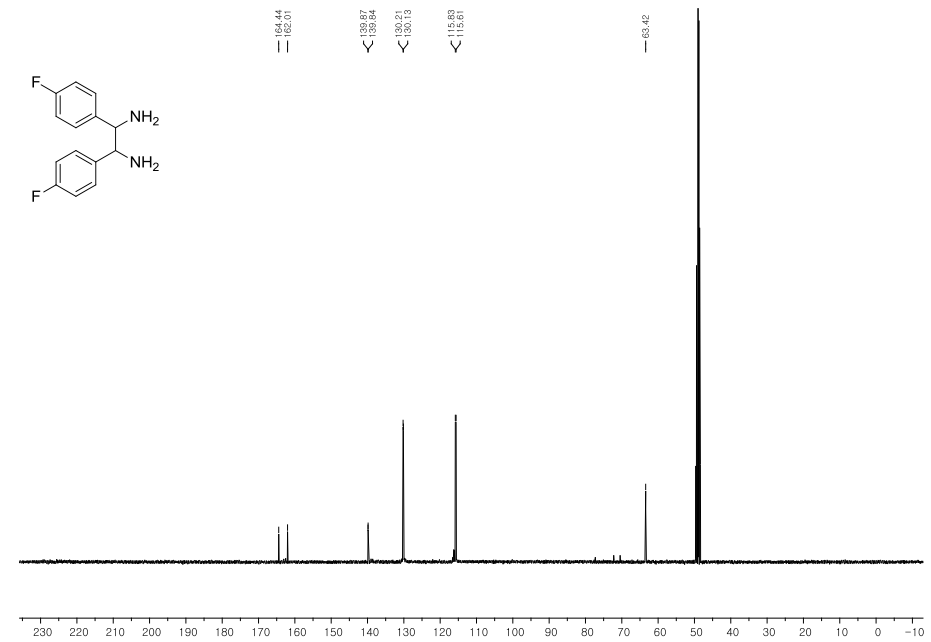
^{1}H NMR spectrum of **3** (400 MHz, MeOD-d_3)



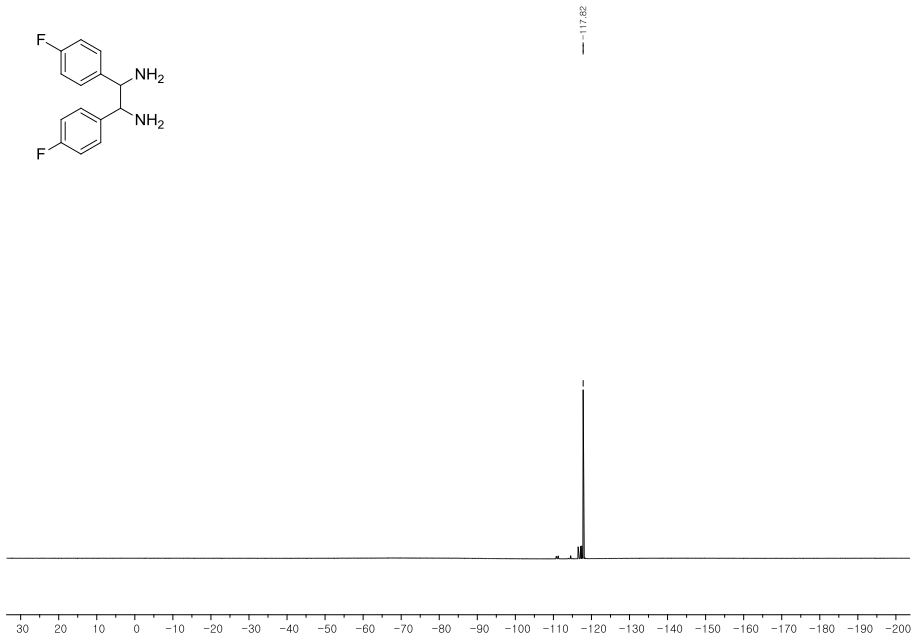
^{13}C NMR spectrum of **3** (101 MHz, MeOD-d_3)



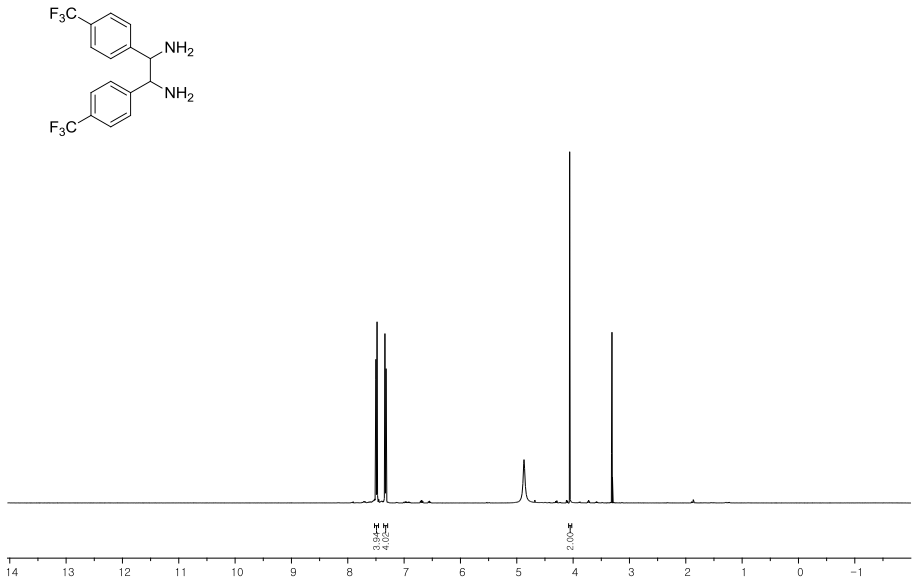
^{1}H NMR spectrum of **4** (400 MHz, MeOD-d_3)



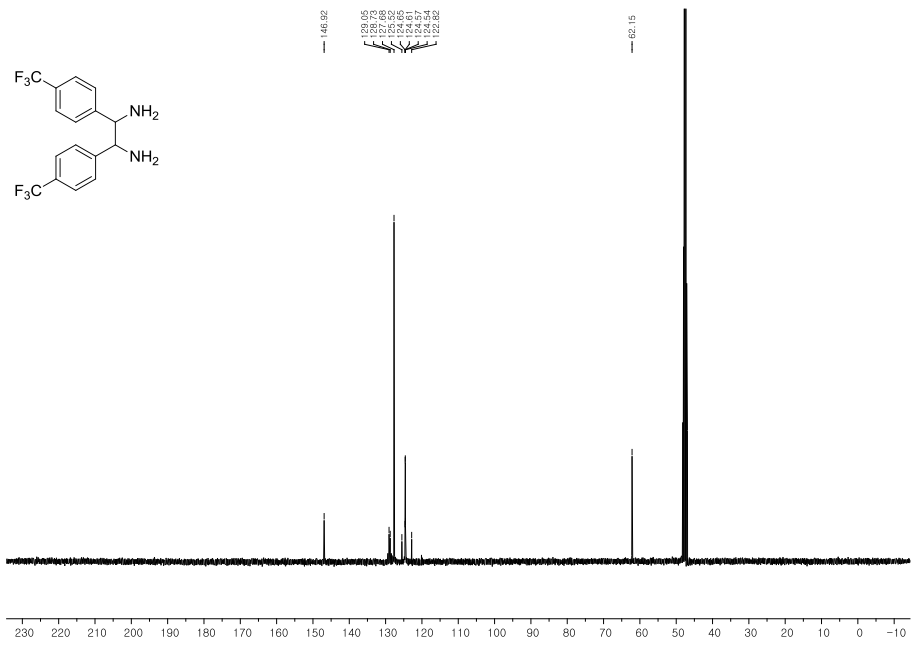
^{13}C NMR spectrum of **4** (101 MHz, MeOD-d_3)



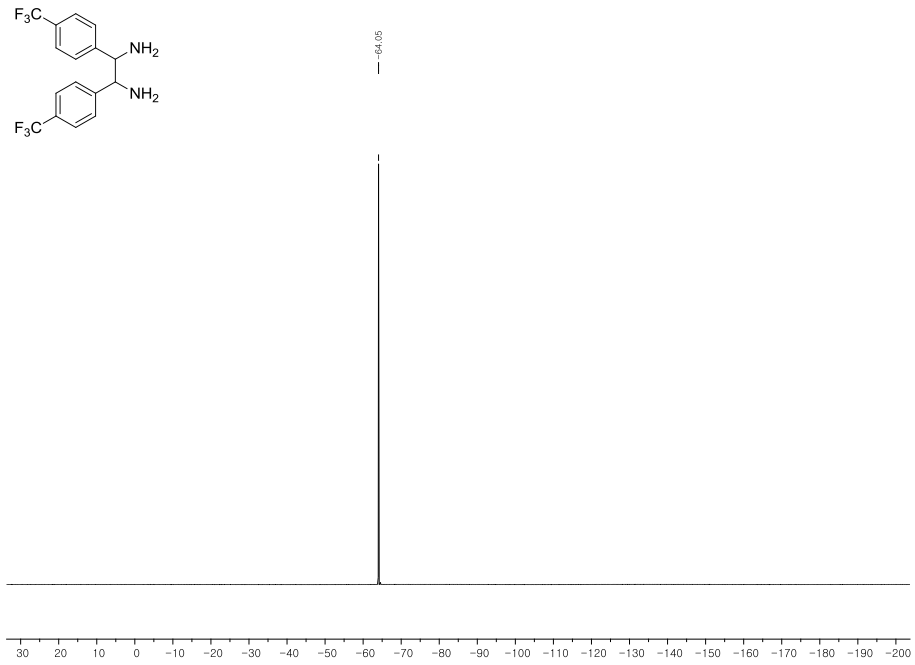
^{19}F NMR spectrum of **4** (376 MHz, MeOD-d_3)



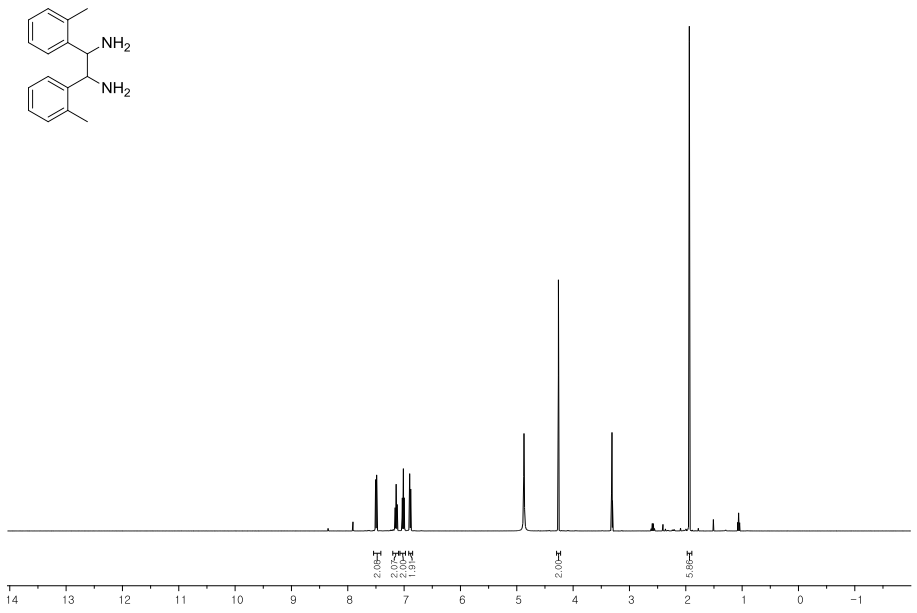
^{1}H NMR spectrum of **5** (400 MHz, MeOD-d_3)



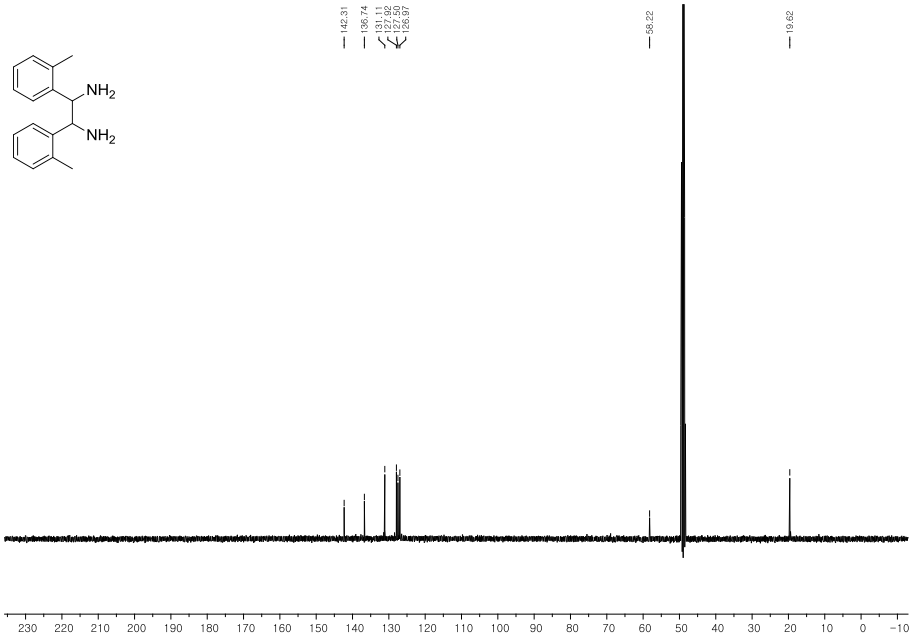
^{13}C NMR spectrum of **5** (101 MHz, MeOD-d_3)



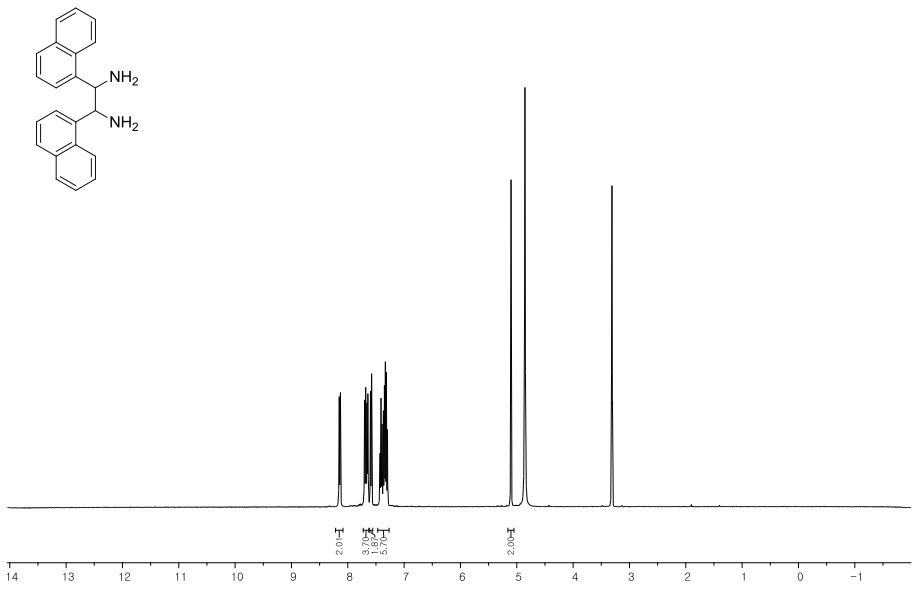
^{19}F NMR spectrum of **5** (376 MHz, MeOD-d_3)



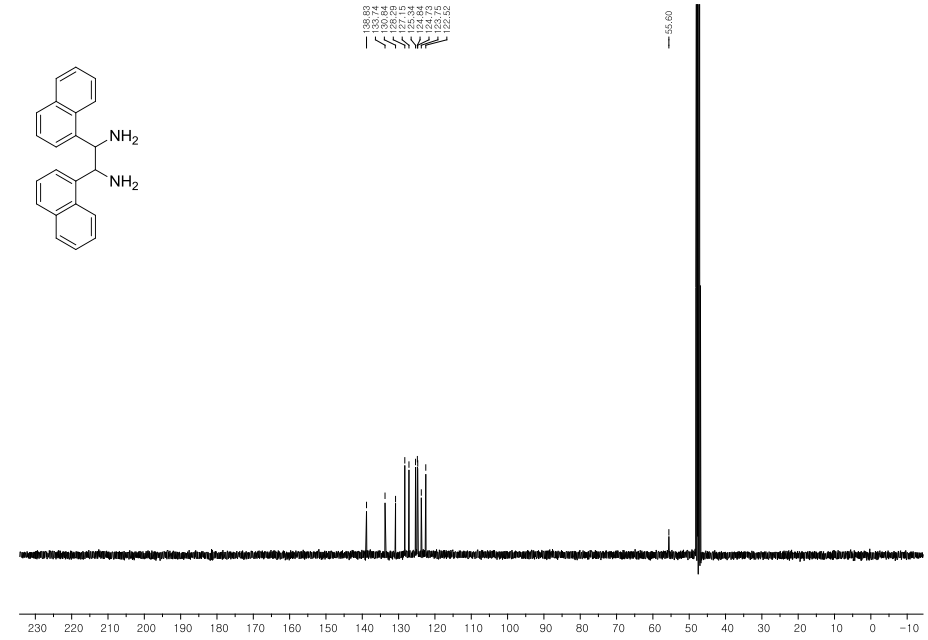
^{1}H NMR spectrum of **6** (400 MHz, MeOD-d_3)



^{13}C NMR spectrum of **6** (101 MHz, MeOD-d_3)



^{1}H NMR spectrum of **7** (400 MHz, MeOD-d_3)



^{13}C NMR spectrum of **7** (101 MHz, MeOD-d_3)

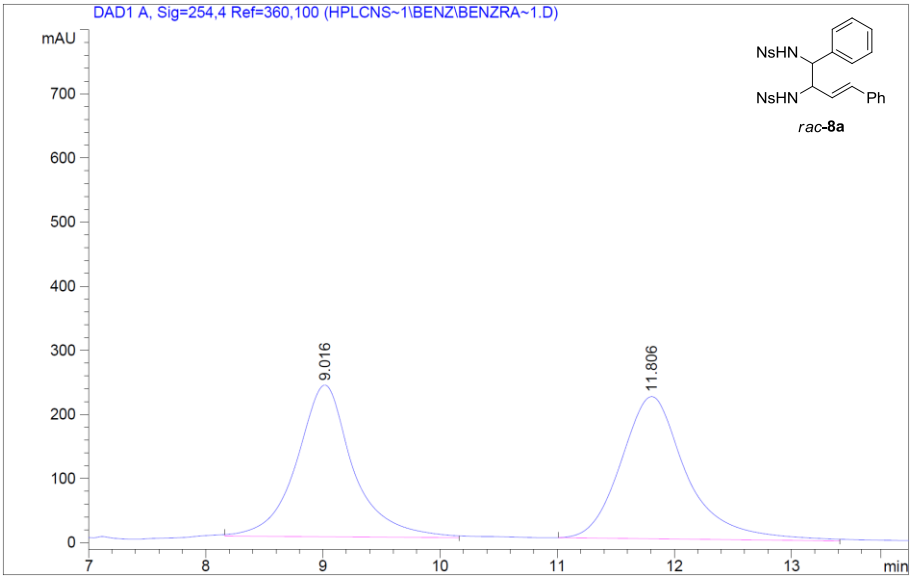
Appendix B

HPLC spectra

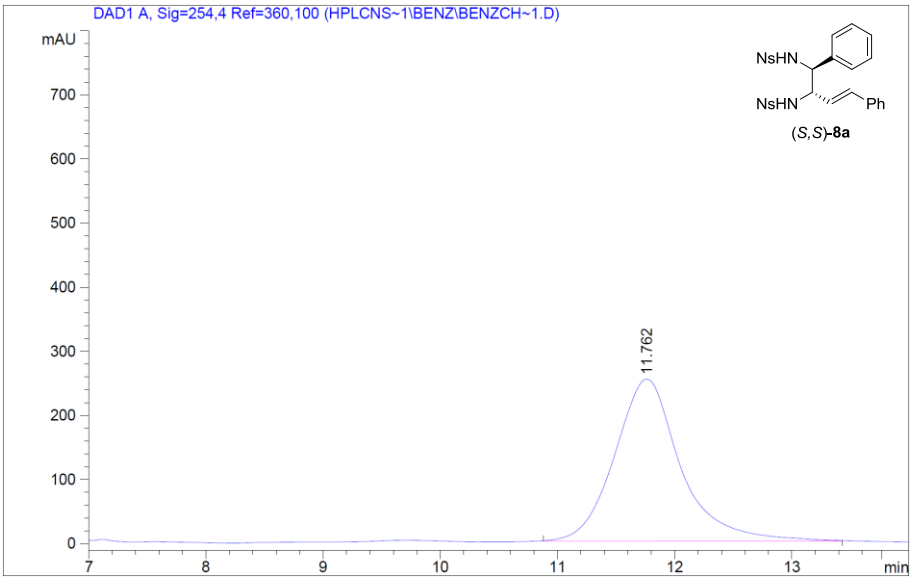
Chapter 1

Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.3 ml/min

rac-**8a**

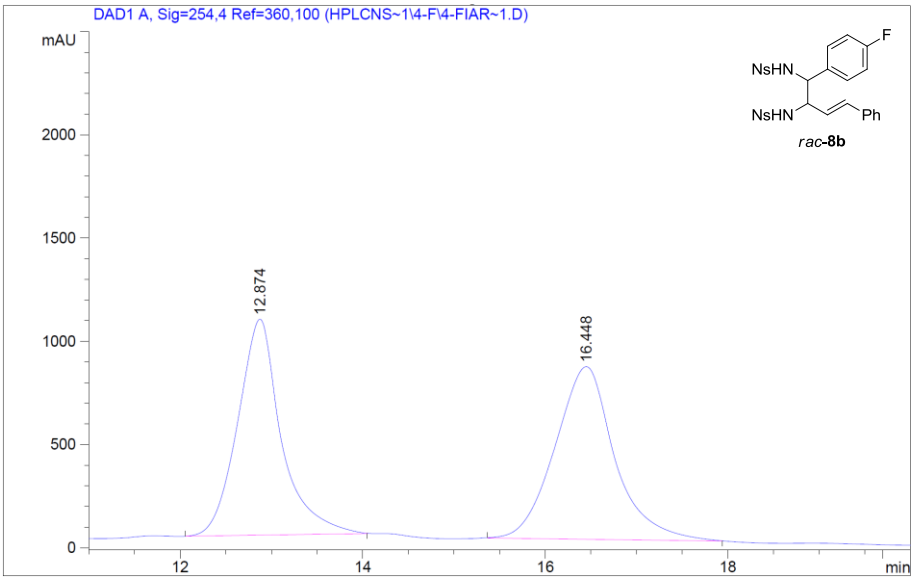


(*S*,*S*)-**8a**

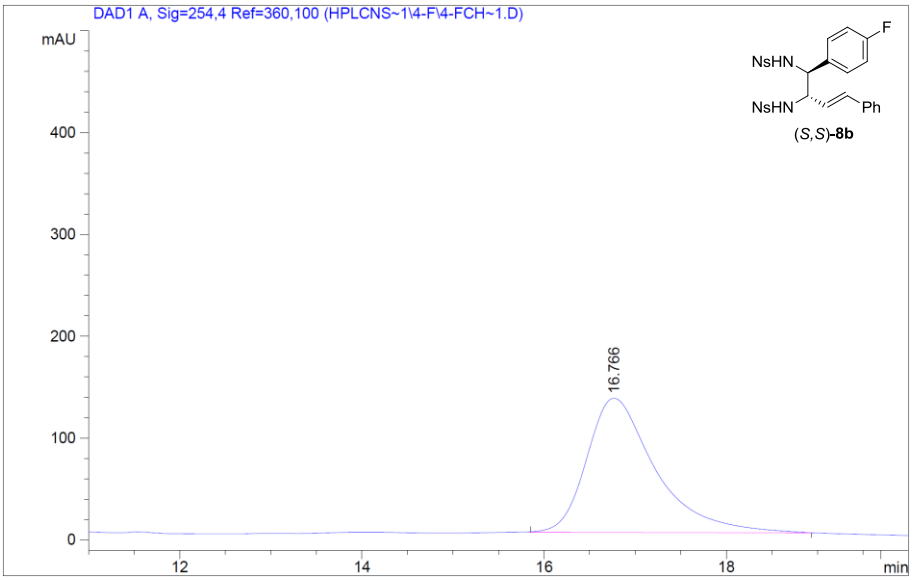


Chiralpak® IA column, 100 % Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.35 ml/min

rac-**8b**

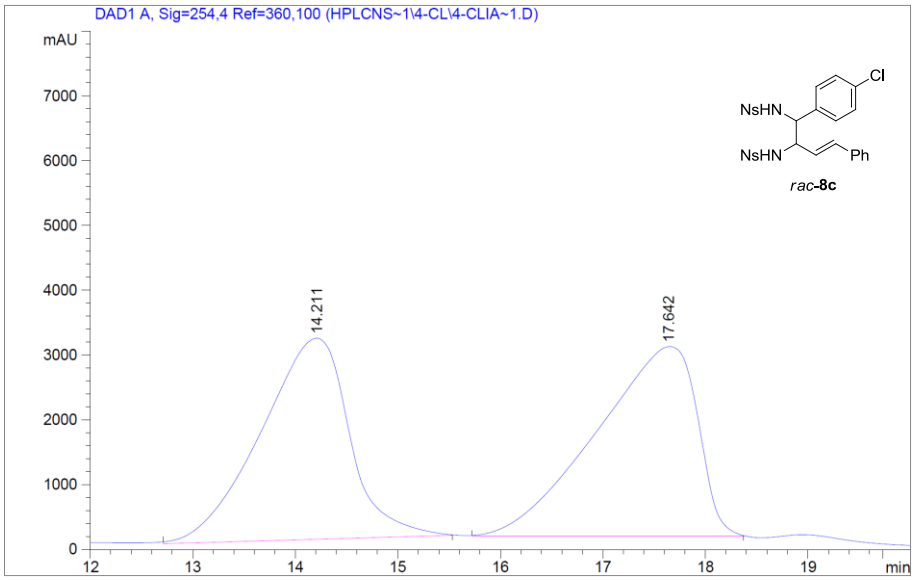


(*S*,*S*)-**8b**

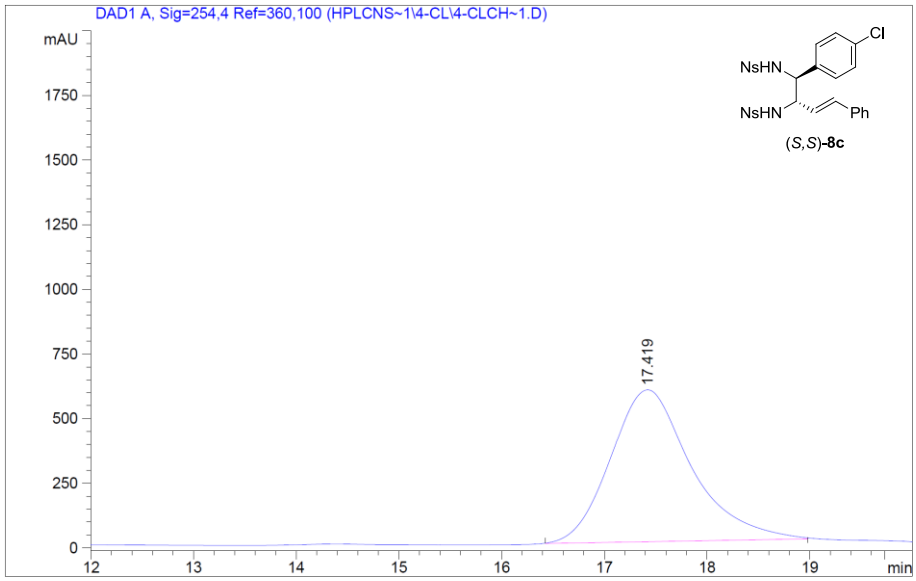


Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.35 ml/min

rac-**8c**

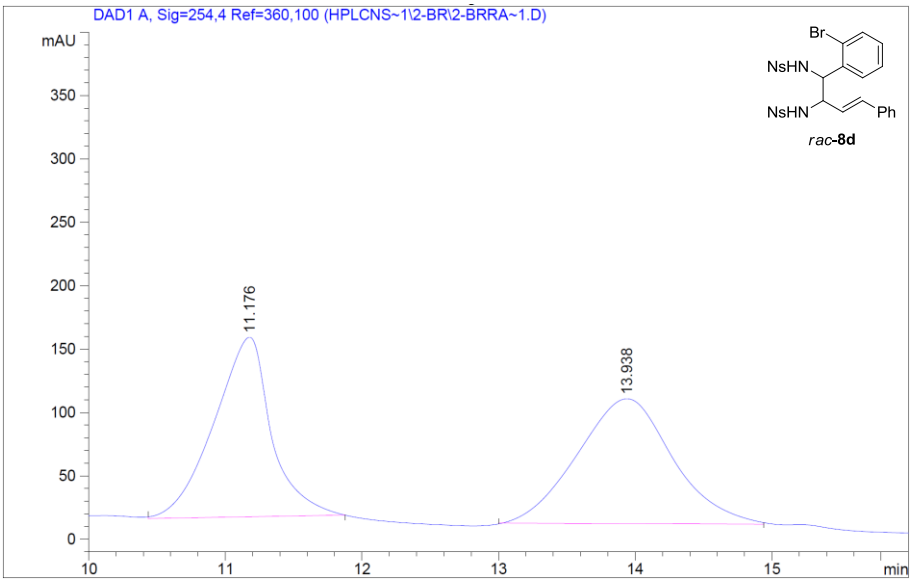


(*S*,*S*)-**8c**

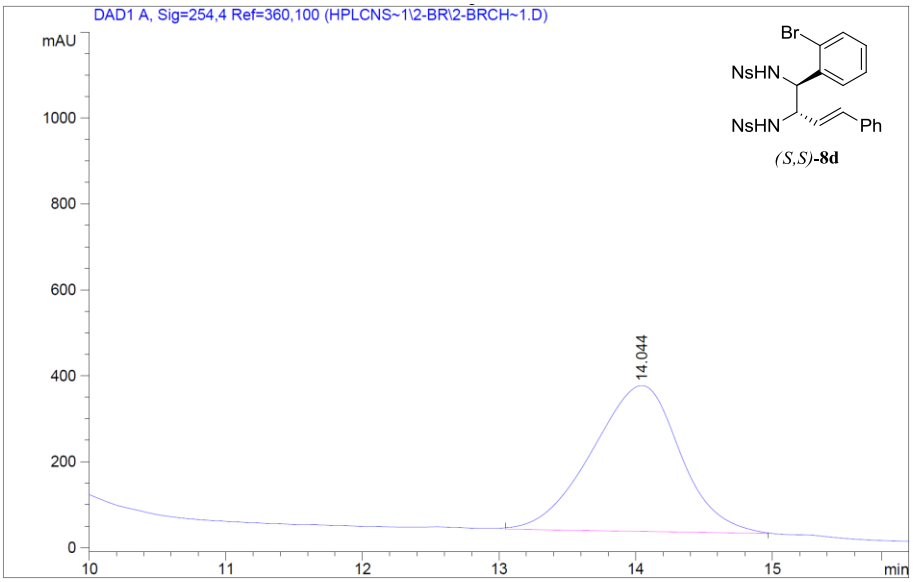


Chiralpak® IA column, 100% Ethyl alcohol + diethyl amine (DEA) 0.1%, 0.35 ml/min

rac-**8d**

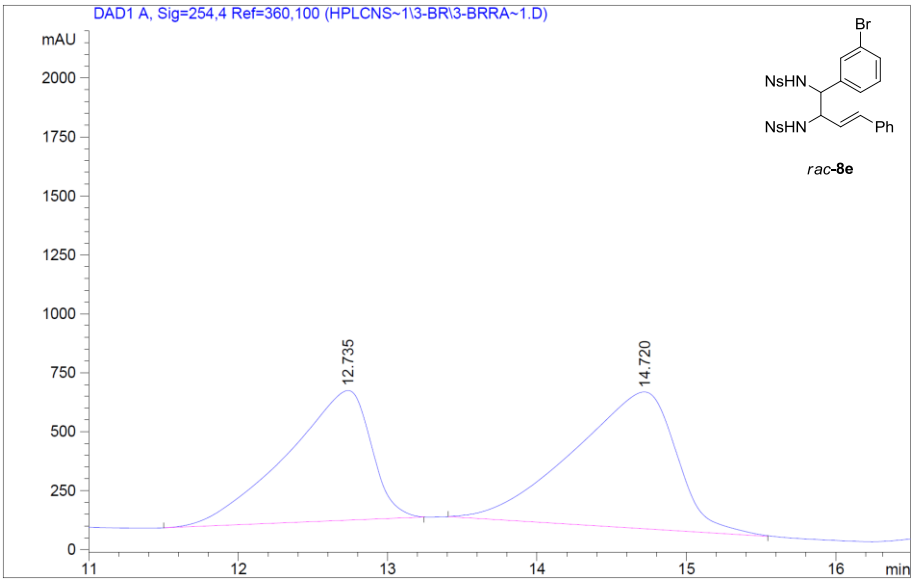


(*S*,*S*)-**8d**

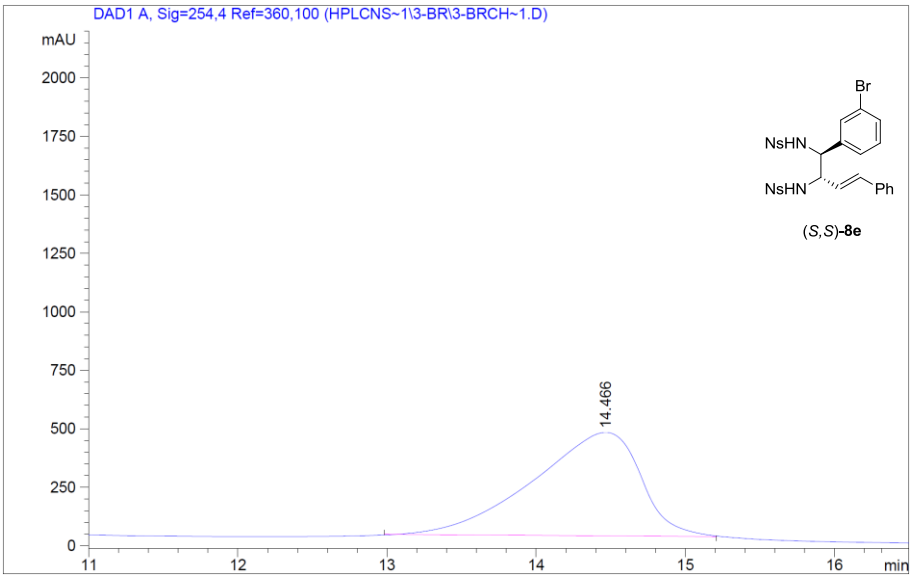


Chiralpak® IA column, 100 % Ethyl alcohol + diethyl amine (DEA) 0.1 %, 0.3 ml/min

rac-**8e**

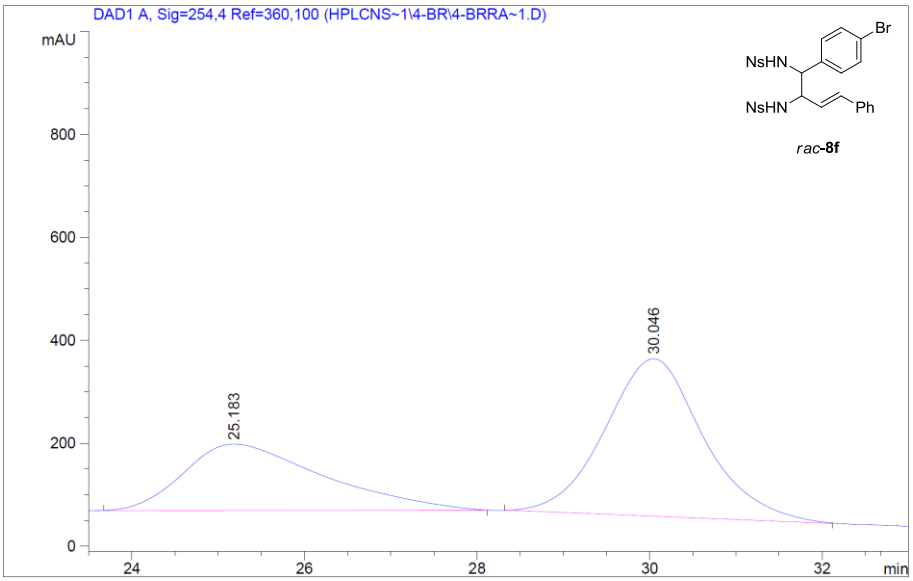


(*S*,*S*)-**8e**

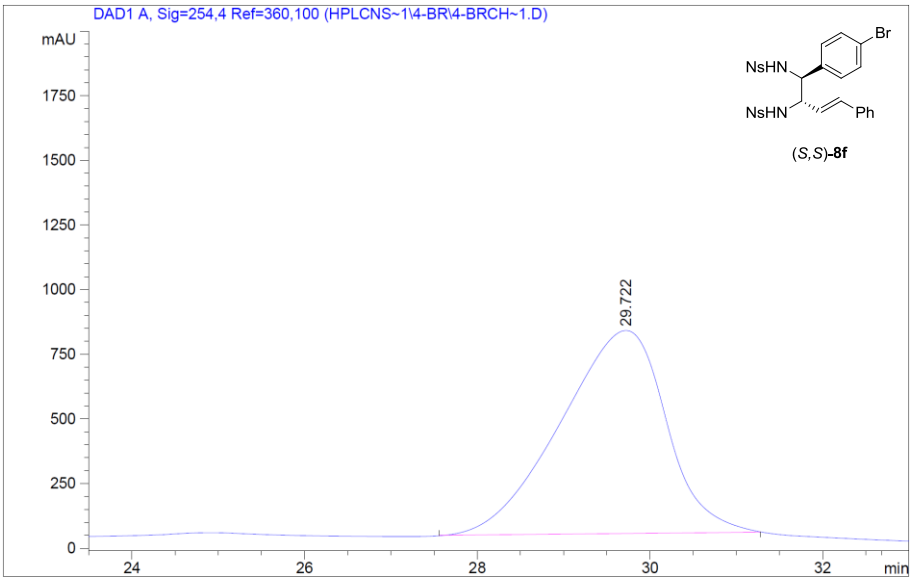


Chiralpak® IA column, 100 % Ethyl alcohol + diethyl amine (DEA) 0.1 %, 0.2 ml/min

rac-**8f**

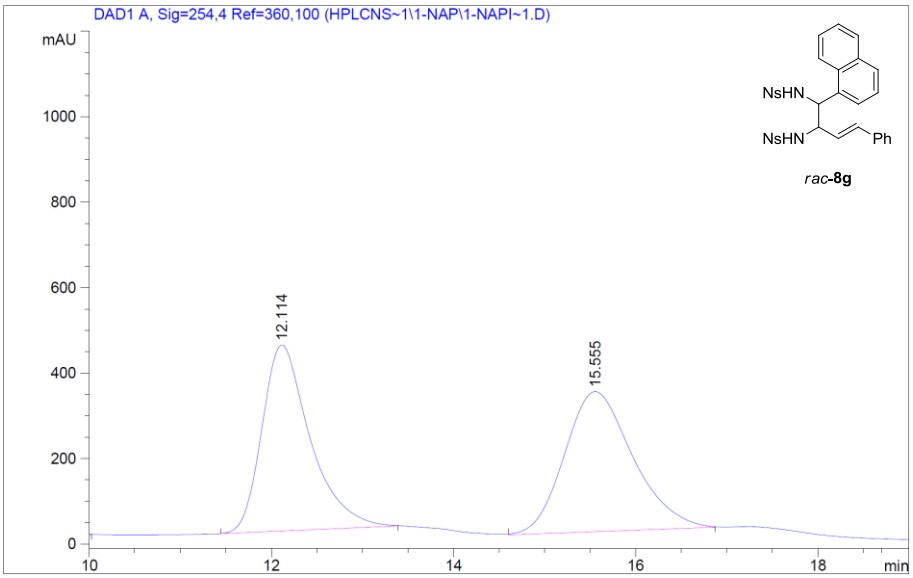


(*S*,*S*)-**8f**

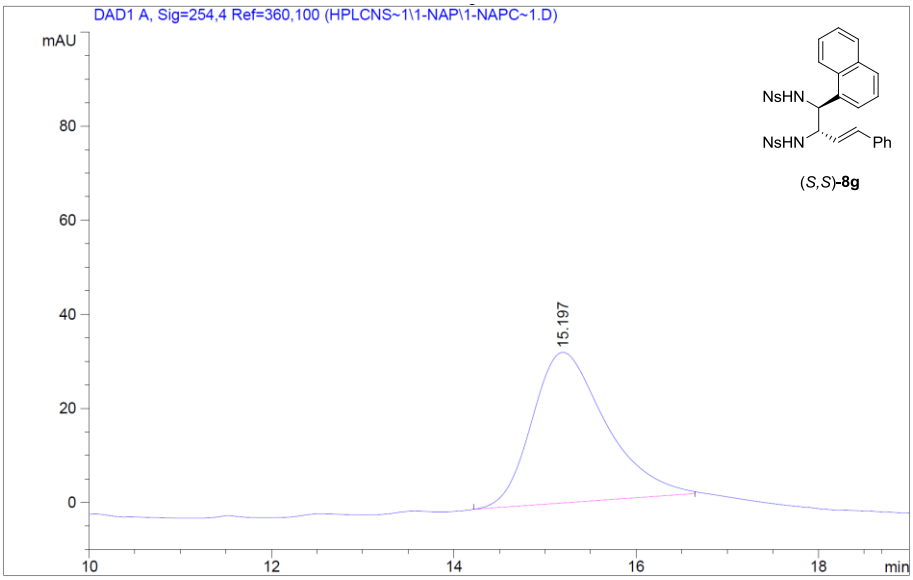


Chiralpak® IA column, 100 % Ethyl alcohol + diethyl amine (DEA) 0.1 %, 0.4 ml/min

rac-**8g**

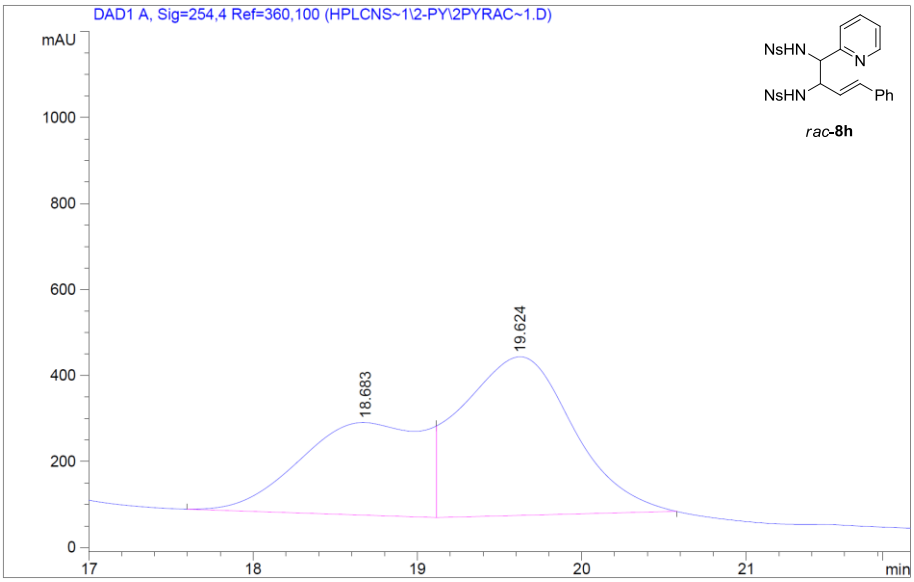


(*S*,*S*)-**8g**

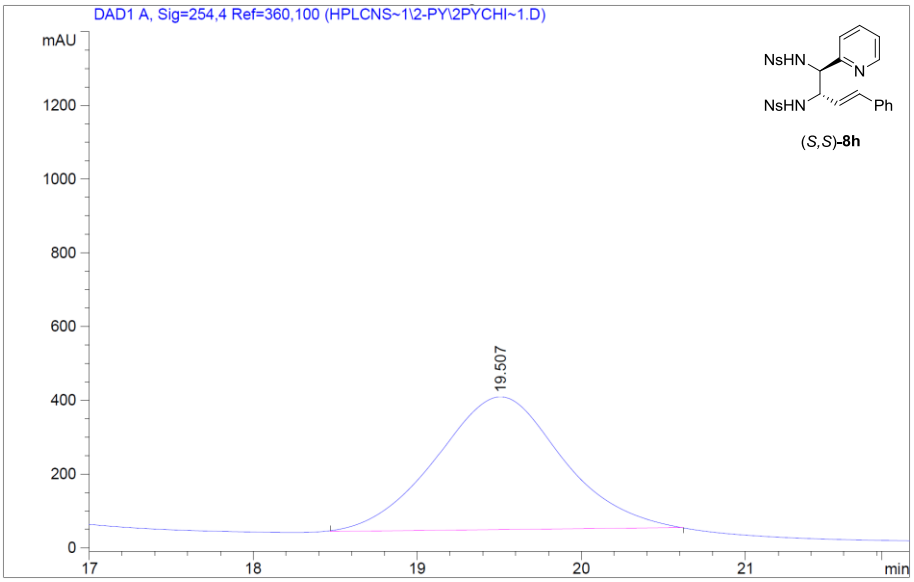


Chiralpak® IA column, 100 % Ethyl alcohol + diethyl amine (DEA) 0.1 %, 0.3 ml/min

rac-**8h**

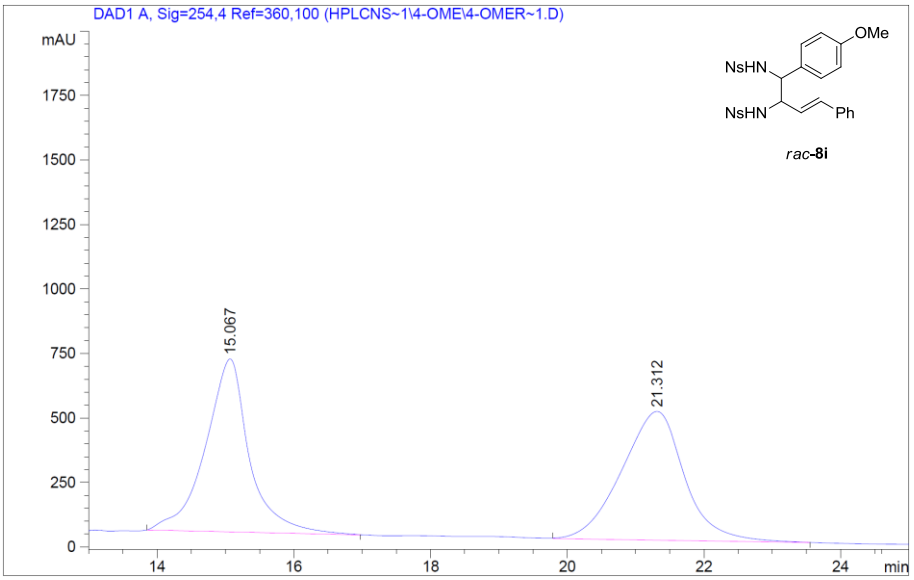


(*S*,*S*)-**8h**

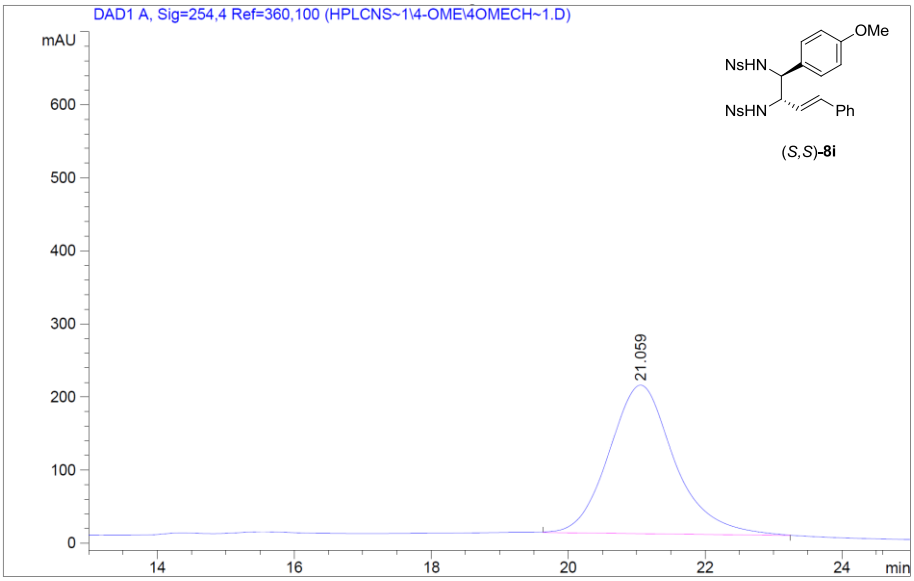


Chiralpak® IA column, 100 % Ethyl alcohol + diethyl amine (DEA) 0.1 %, 0.35 ml/min

rac-**8i**

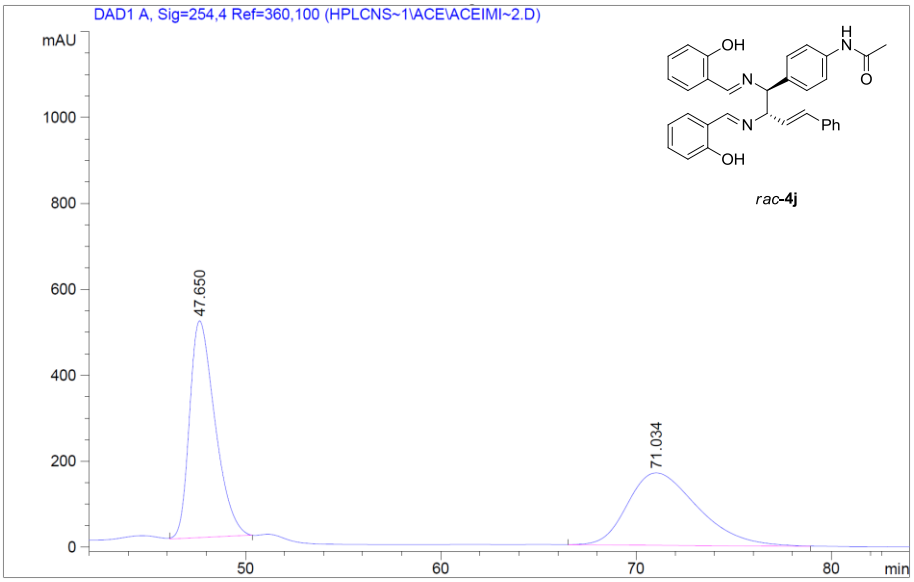


(S,S)-**8i**

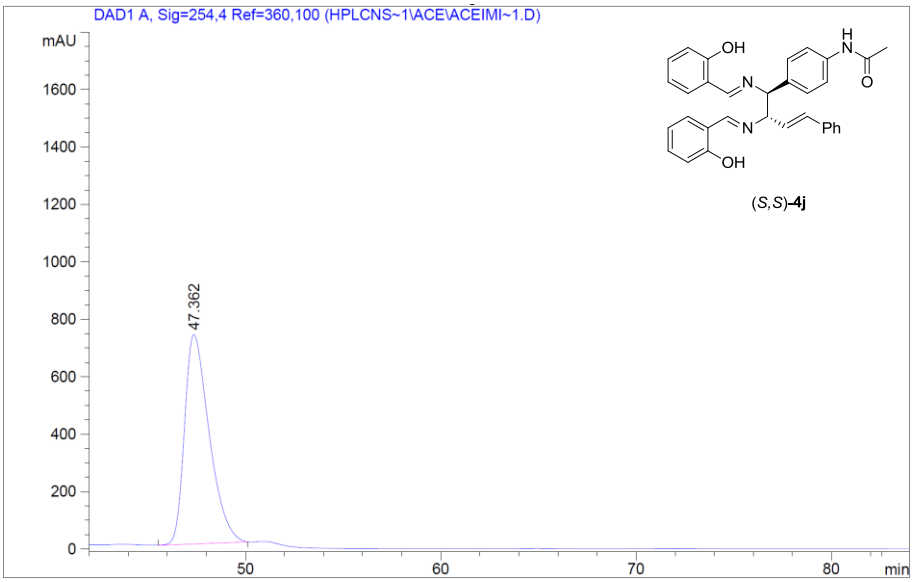


Chiralpak® IA column, 100 % Ethyl alcohol + diethyl amine (DEA) 0.1 %, 0.3 ml/min

rac-**4j**



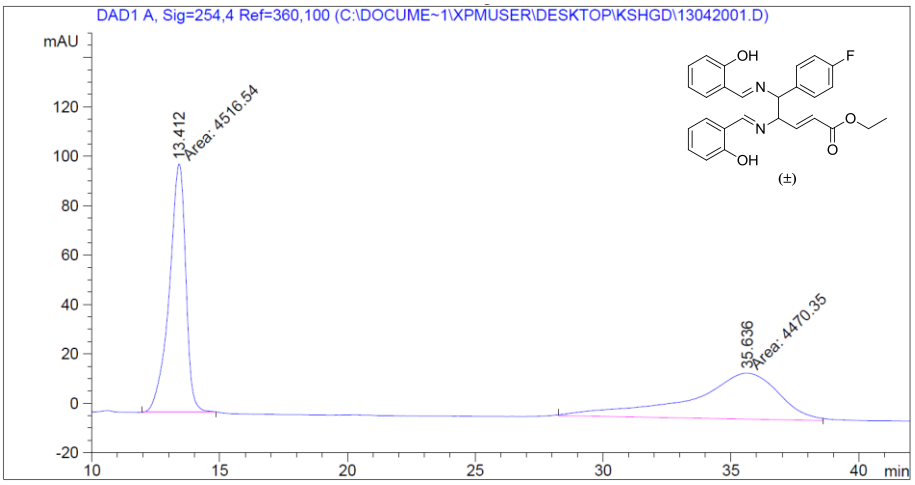
(*S,S*)-**4j**



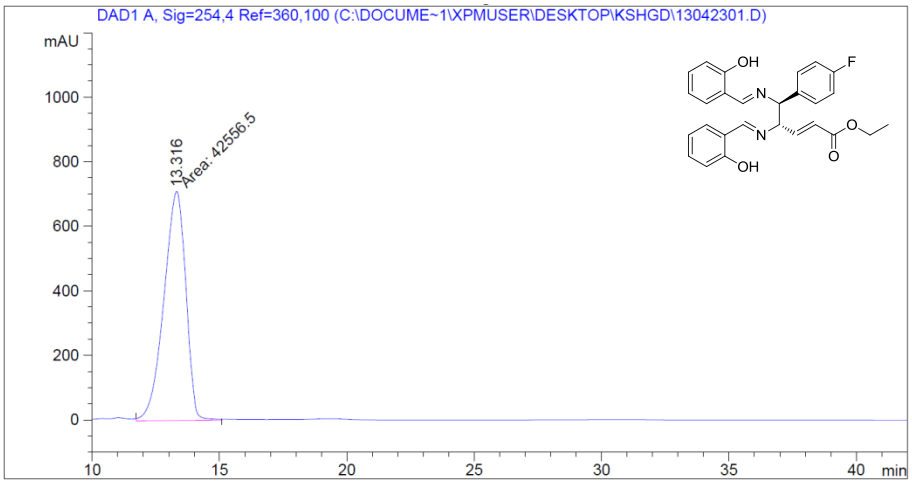
Chapter 2

Chiralpak® IA column, *n*-Hexane : EtOH = 7:3, Flow rate = 1.0 ml/min

Rac-**3a**

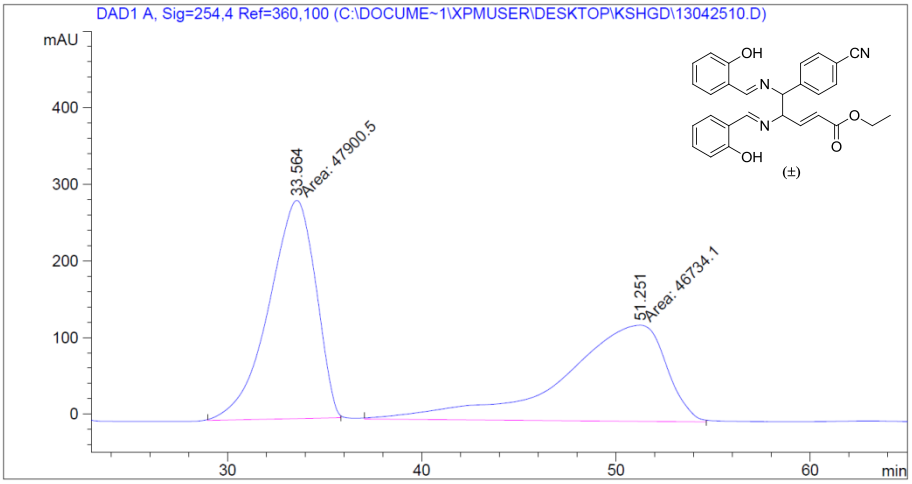


(*S*,*S*)-**3a**

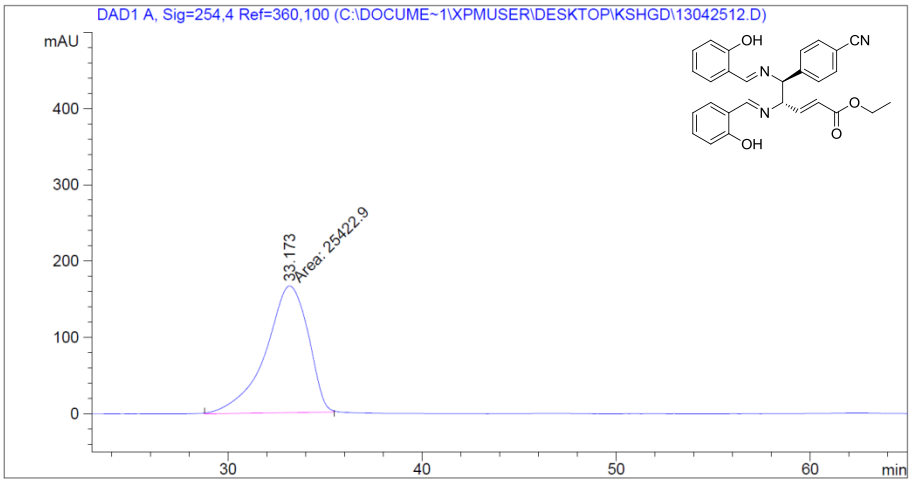


Chiralpak® IA column, *n*-Hexane : EtOH = 7:3, Flow rate = 1.0 ml/min

***Rac*-3b**

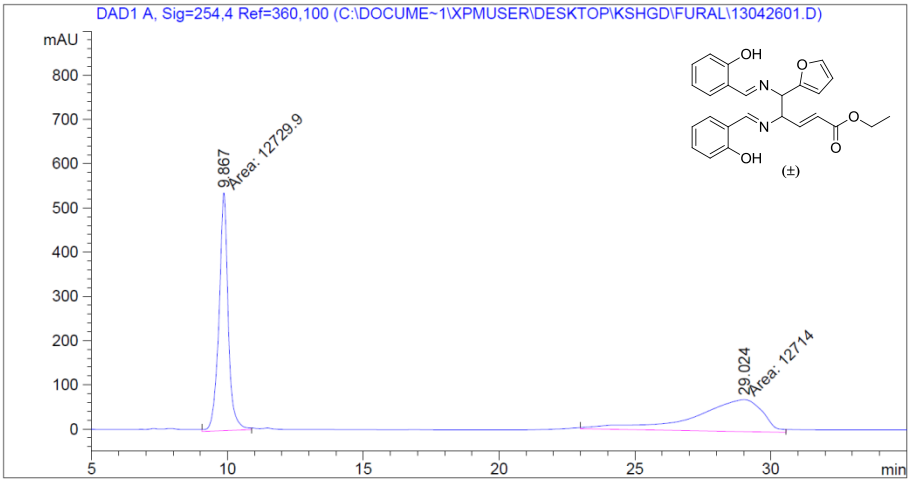


(*S*,*S*)-**3b**

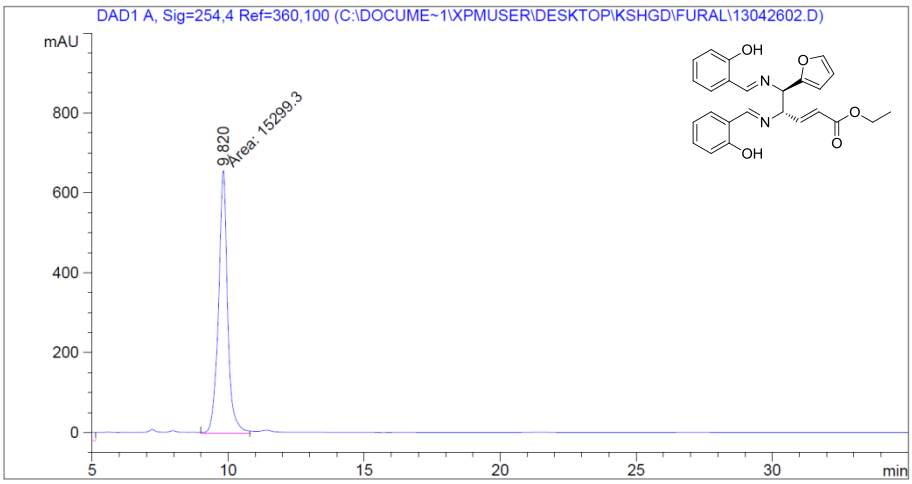


Chiralpak® IA column, *n*-Hexane : EtOH = 7:3, Flow rate = 1.0 ml/min

Rac-**3c**

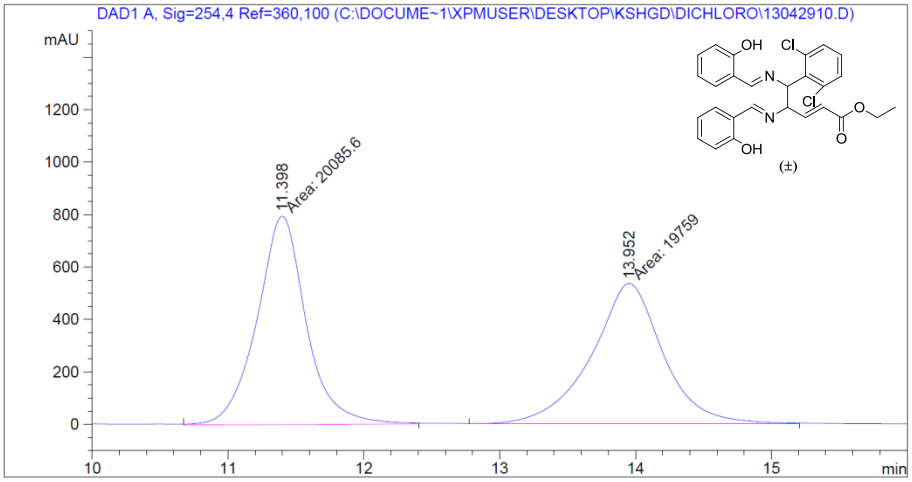


(*S*,*S*)-**3c**

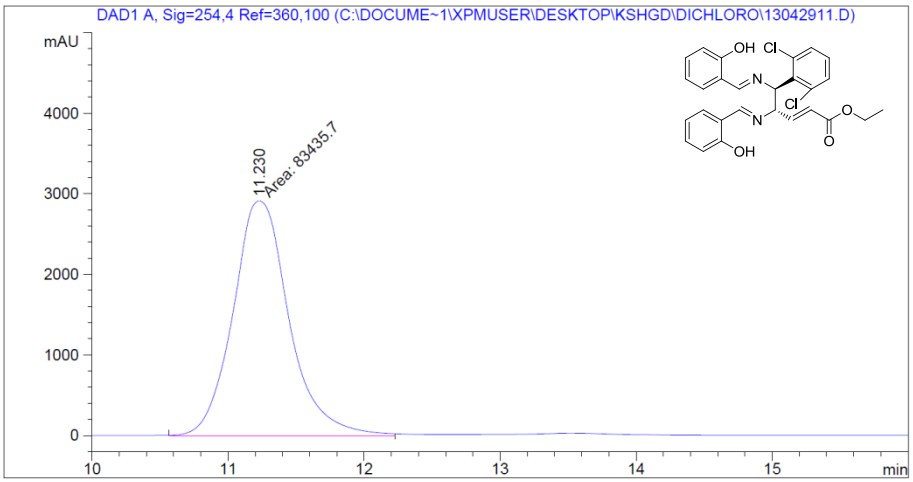


Chiralpak® IA column, *n*-Hexane : EtOH = 7:3, Flow rate = 1.0 ml/min

Rac-**3d**

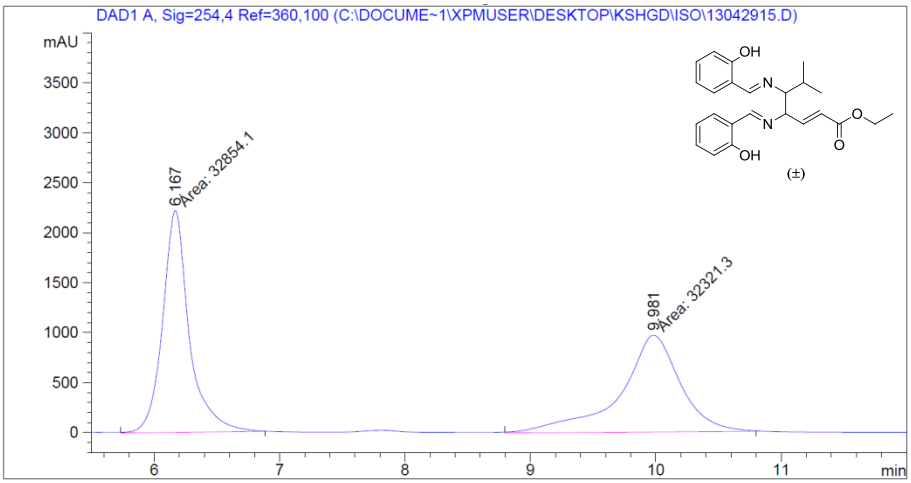


(*S*,*S*)-**3d**

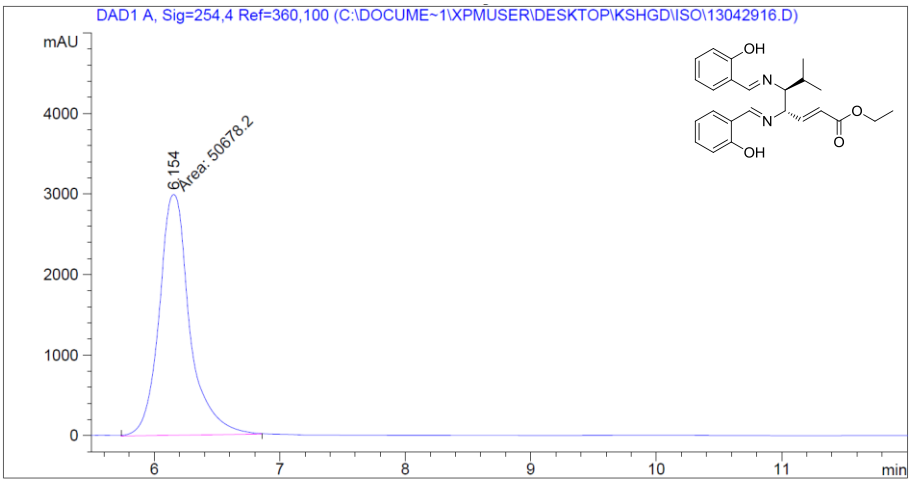


Chiralpak® IA column, *n*-Hexane : EtOH = 8:2, Flow rate = 1.0 ml/min

***Rac*-3e**

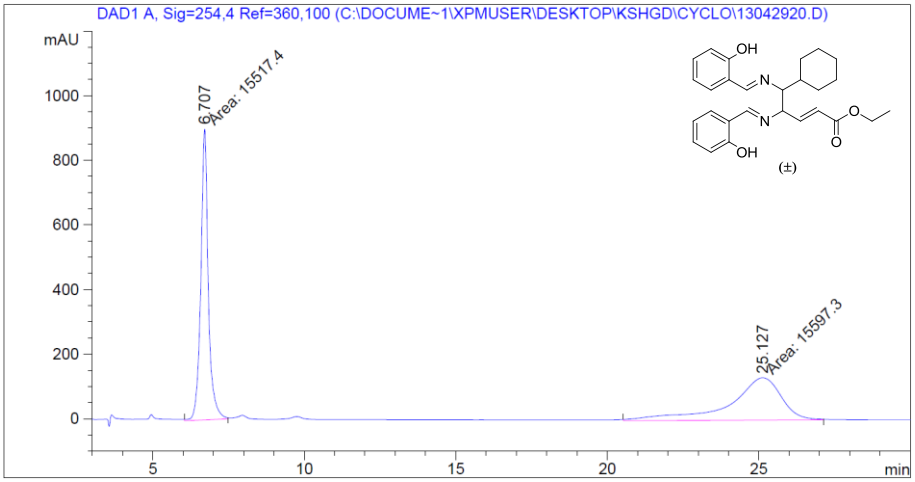


(*S*,*S*)-3e

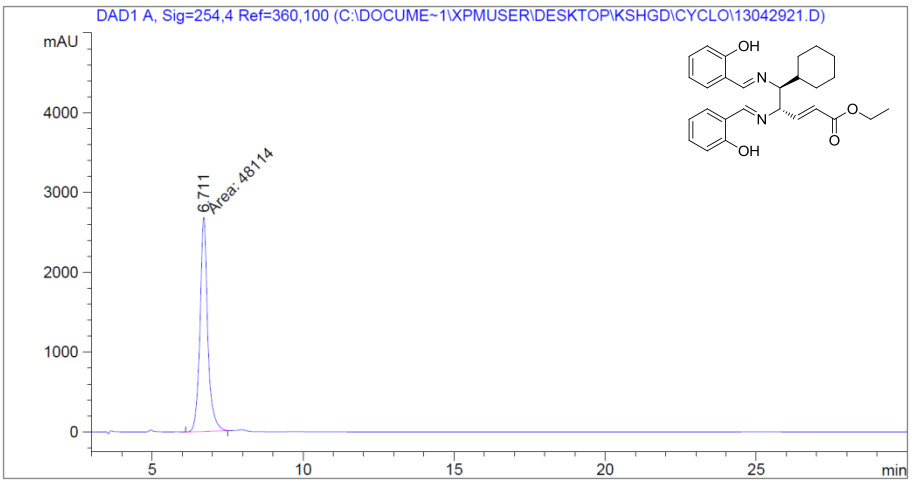


Chiralpak® IA column, *n*-Hexane : EtOH = 8:2, Flow rate = 1.0 ml/min

Rac-**3f**

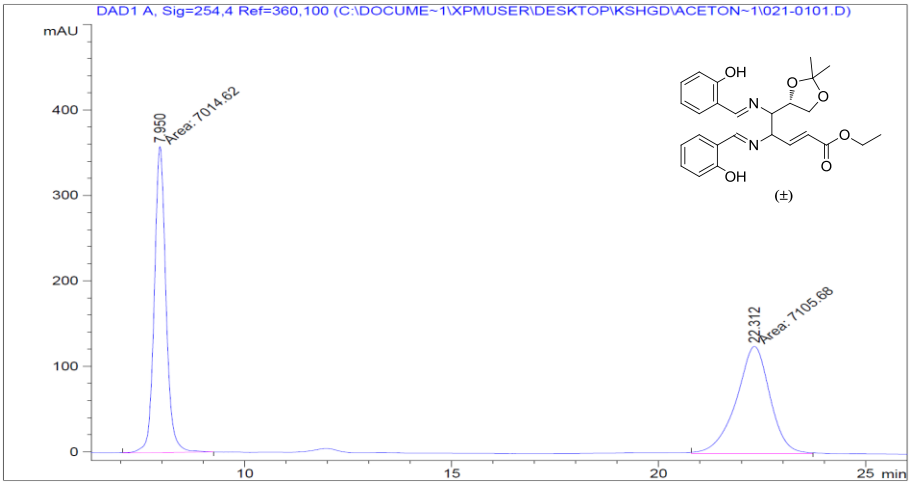


(*S*,*S*)-**3f**

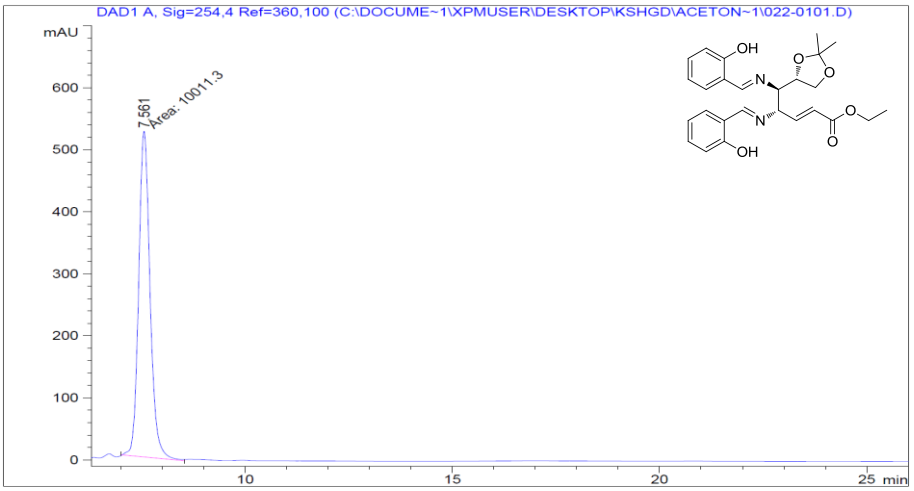


Chiralpak® IA column, *n*-Hexane : EtOH = 7:3, Flow rate = 1.0 ml/min

Rac-**3g**



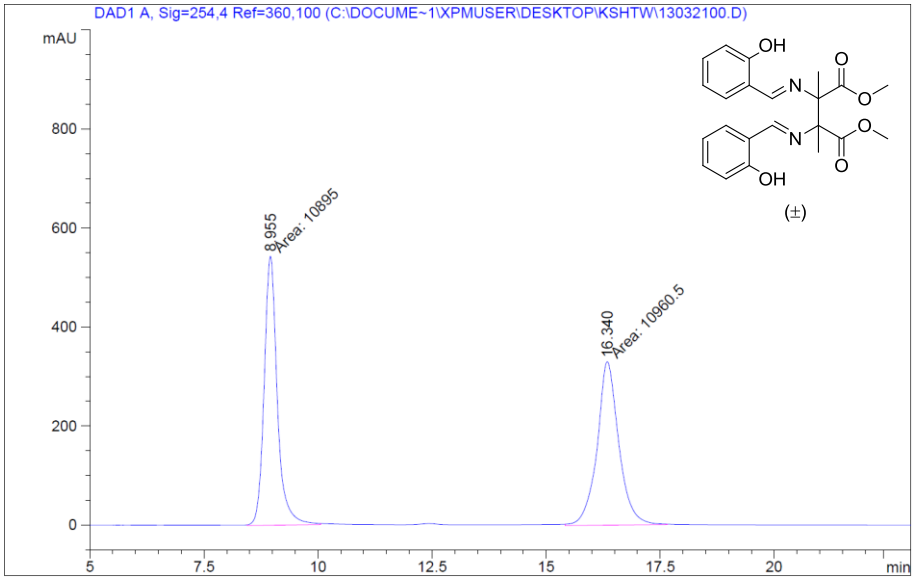
(*S*,*R*)-**3g**



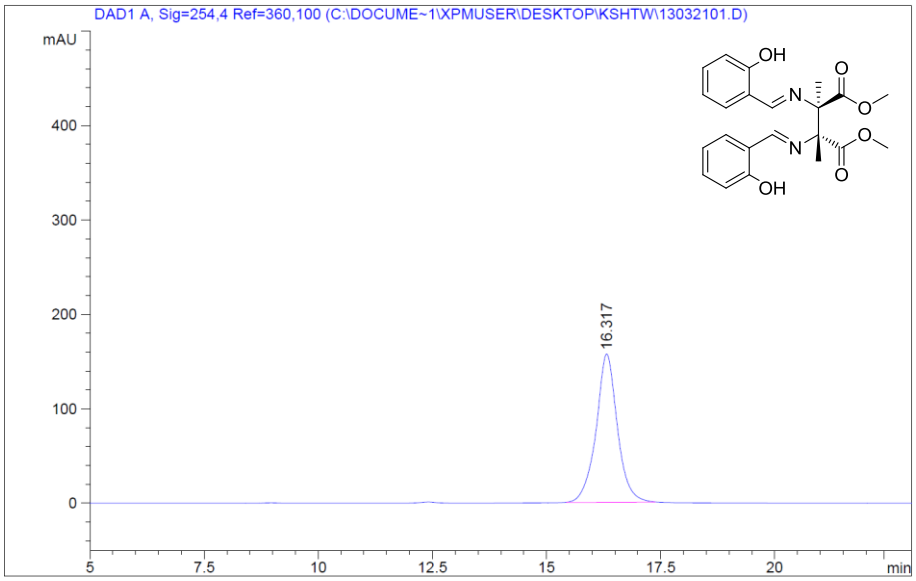
Chapter 3

Chiralpak® IA column, *n*-Hexane : *i*-PrOH = 90:10, Flow rate = 1.0 ml/min

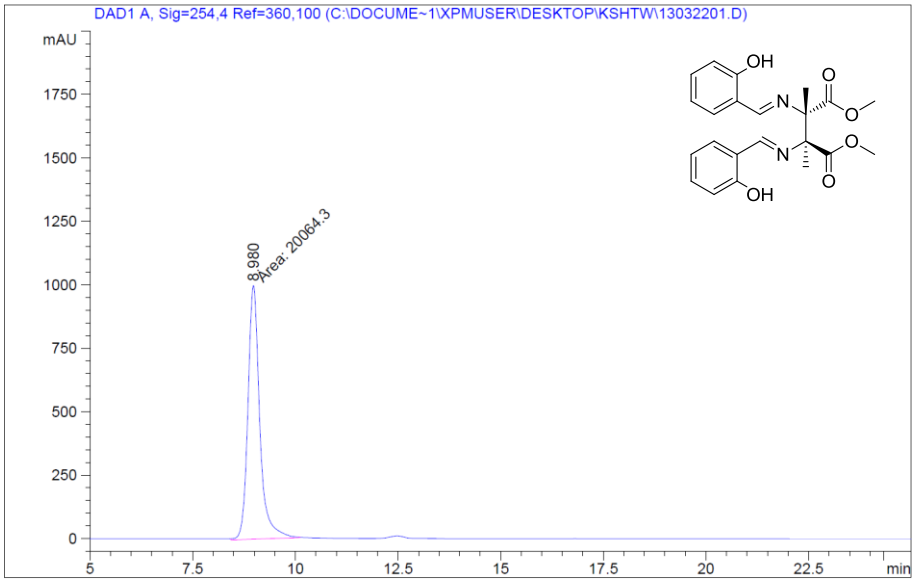
Rac-**3**



(*R*,*R*)-**3**



(*S*,*S*)-**3**

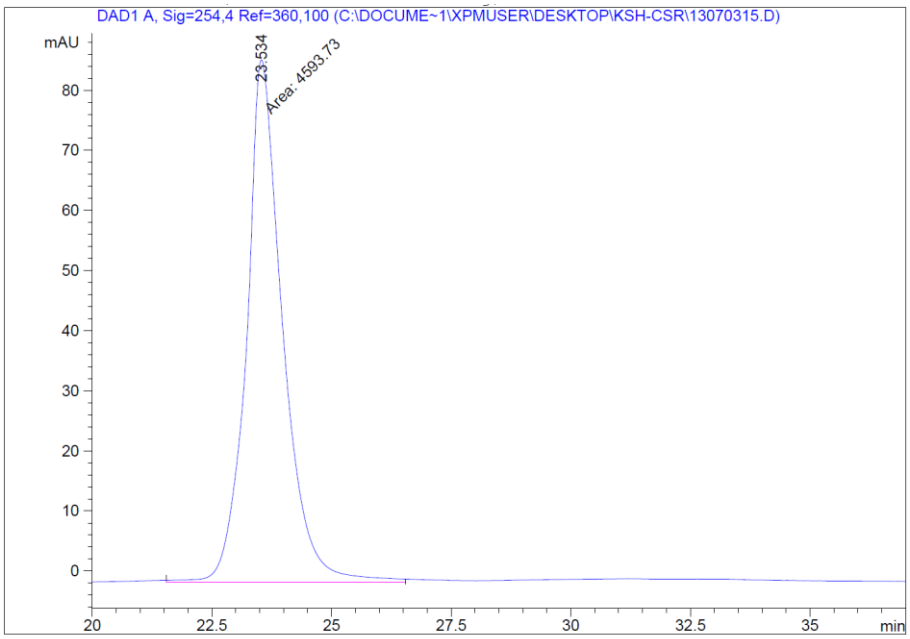

DAD1 A, Sig=254,4 Ref=360,100 (C:\DOCUME~1\XPMUSER\DESKTOP\KSHTW\13032201.D)
mAU
1750
1500
1250
1000
750
500
250
0
8.980
Area: 20064.3
5
7.5
10
12.5
15
17.5
20
22.5
min
OH
N
O
O
N
O
OH

Chapter 4

LC data

Chiralpak® IA column, *n*-hexane:*iso*-propyl alcohol = 9:1, 1.0 ml/min

1. >99% ee



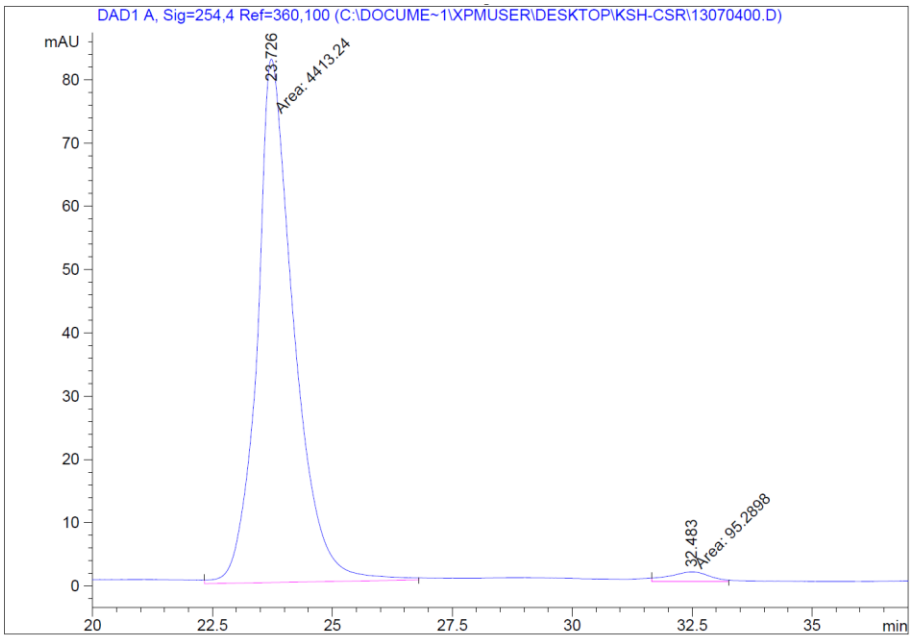

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.534 MM    0.8805 4593.73096   86.95110 100.0000
```

2. 95.7% ee



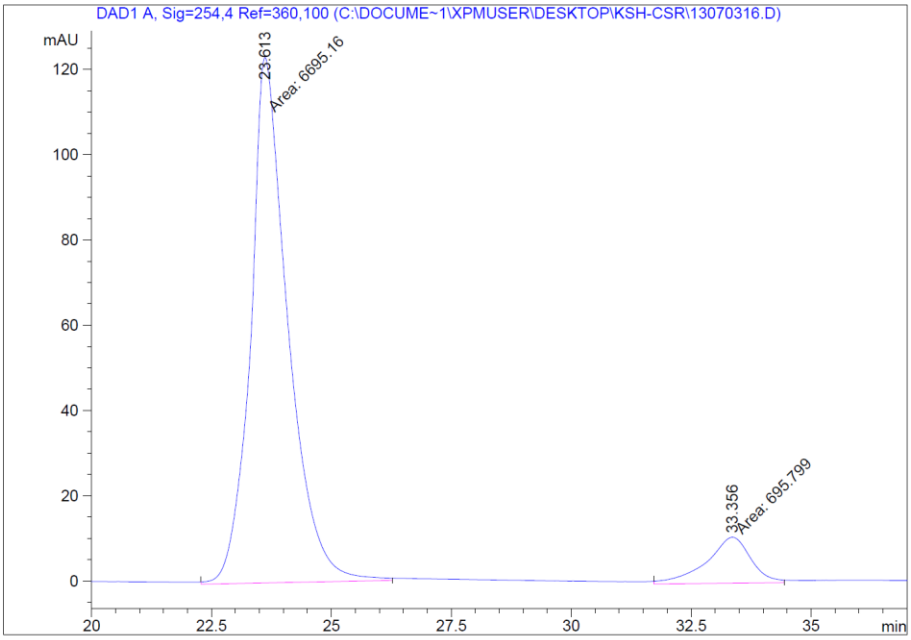

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.726 MM    0.8894 4413.23828   82.70339  97.8865
   2  32.483 MM    1.0067   95.28983    1.57767   2.1135
```

3. 81.2% ee



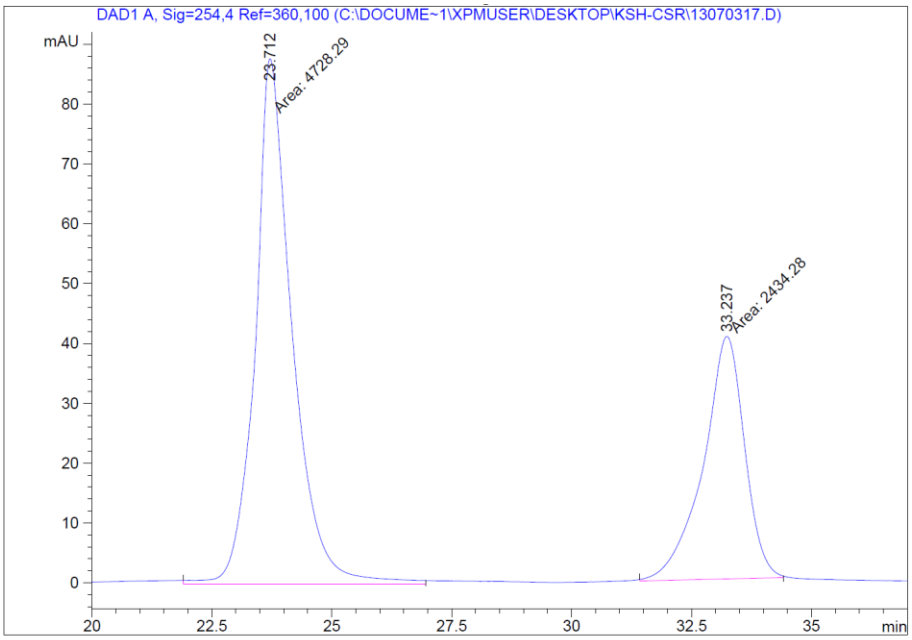

```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.613 MM    0.9053 6695.16064  123.25822  90.5858
   2  33.356 MM    1.0754  695.79858   10.78368   9.4142
```

4. 32.0% ee



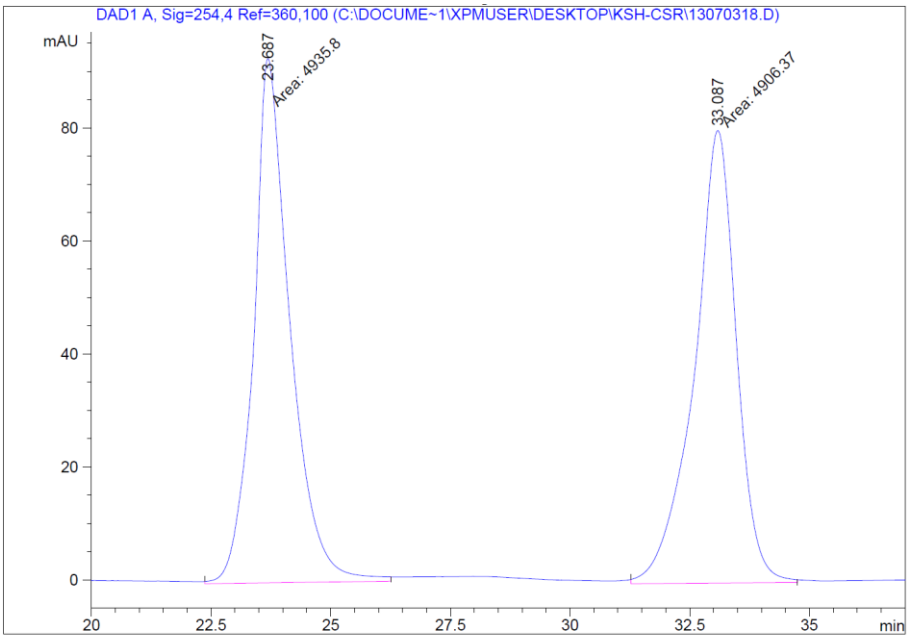

```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.712 MM    0.8973 4728.29102   87.82693  66.0139
   2  33.237 MM    1.0008 2434.28223   40.53696  33.9861
```

5. 0.3% ee




```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.687 MM    0.8868 4935.80127   92.76324  50.1495
   2  33.087 MM    1.0214 4906.36963   80.05774  49.8505
```

Appendix C

Computational data

Chapter 2

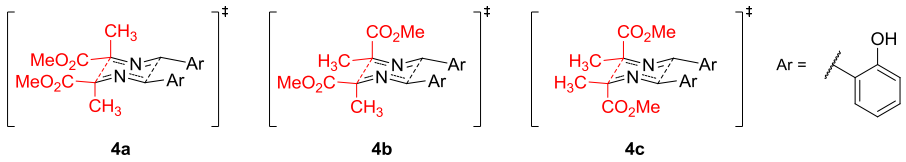
In Scheme II-2, II-3,

Molecules	Energy (hartree)	E+ZPVE (hartree)	$\Delta H_{298.15K}$ (hartree)	Imaginary frequency (cm^{-1})
4x	-1341.372087	0.454791925	-1340.894890	
4y	-1418.777069	0.488232908	-1418.264757	
4z	-1454.911729	0.478609941	-1454.408260	
4w	-1341.798241	0.481893163	-1341.291604	
5x	-1341.343196	0.450728623	-1340.869500	*i* 203.636
5y	-1418.749933	0.484338221	-1418.240980	*i* 205.911
5z	-1454.886743	0.475212531	-1454.386236	*i* 247.939
5w	-1341.767938	0.478923557	-1341.263867	*i* 228.404
6x	-1341.382937	0.454273700	-1340.906352	
6y	-1418.785293	0.487841592	-1418.273480	
6z	-1454.924200	0.478264978	-1454.421228	
6w	-1341.812763	0.482813597	-1341.305525	

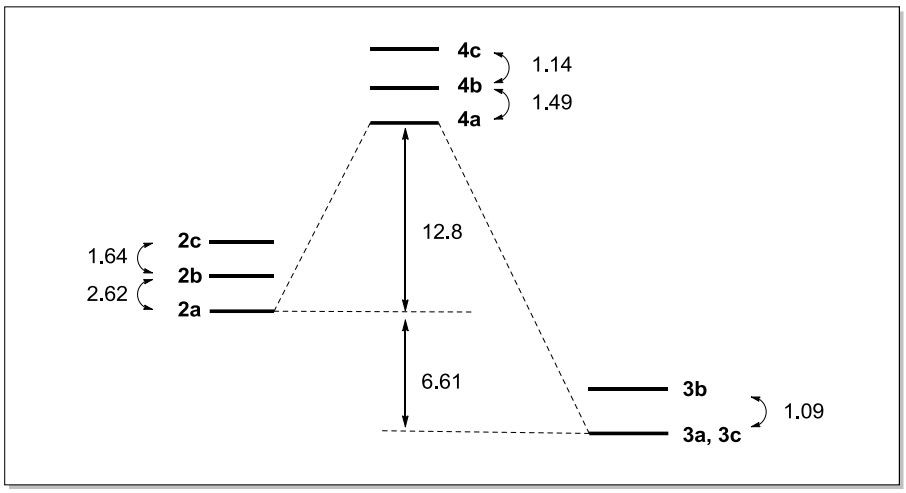
B3LYP/6-31G (d) level

Chapter 3

Transition state of compound 4 (Figure III-2)



4a 4b 4c

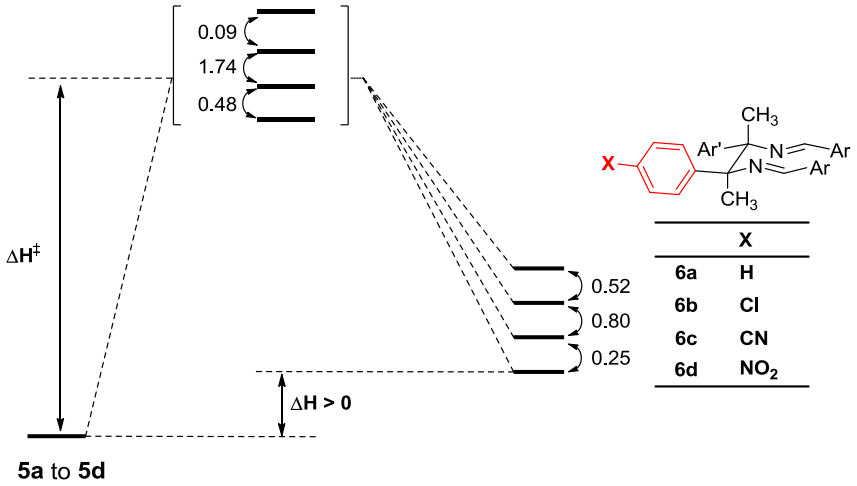


Enthalpy values in kcal/mol.

Molecules	Energy (hartree)	E+ZPVE (hartree)	$\Delta H_{298.15K}$ (hartree)	Imaginary frequency (cm^{-1})
2a	-1413.627618	-1413.194171	-1413.164382	
2b	-1413.624778	-1413.190705	-1413.160212	
2c	-1413.621111	-1413.187197	-1413.157592	
3a, 3c	-1413.638968	-1413.204239	-1413.174917	
3b	-1413.636684	-1413.203042	-1413.173175	
4a	-1413.605623	-1413.173733	-1413.144003	*i* 265.644
4b	-1413.603385	-1413.171061	-1413.141625	*i* 277.903
4c	-1413.601180	-1413.169660	-1413.139813	*i* 277.864

B3LYP/6-31G (d) level

The effect of para-substituents on acetophenone (Scheme III-2)



Enthalpy values in kcal/mol.

Molecules		Energy (hartree)	E+ZPVE (hartree)	$\Delta H_{298.15K}$ (hartree)	$\Delta H‡$ (kcal/mol) / ΔH (kcal/mol)
	5a	-1419.999729	-1419.488580	-1419.458128	16.1
H	**TS-a**	-1419.969228	-1419.461794	-1419.432493	
	6a	-1419.990193	-1419.479841	-1419.450020	5.09
	5b	-2339.191082	-2338.699175	-2338.666259	16.0
Cl	**TS-b**	-2339.161835	-2338.673315	-2338.640794	
	6b	-2339.182350	-2338.69132	-2338.658987	4.56
	5c	-1604.483396	-1603.975129	-1603.940979	14.2
CN	**TS-c**	-1604.457011	-1603.951937	-1603.918286	
	6c	-1604.475962	-1603.968511	-1603.934976	3.77
	5d	-1828.999027	-1828.482670	-1828.447075	13.8
NO_2	**TS-d**	-1828.973518	-1828.460264	-1828.425153	
	6d	-1828.992002	-1828.476485	-1828.441466	3.52

B3LYP/6-31G (d) level

In Scheme III-3,

Molecules	Energy (hartree)	E+ZPVE (hartree)	$\Delta H_{298.15K}$ (hartree)	Imaginary frequency (cm^{-1})
2	-1413.627618	-1413.194171	-1413.164382	
3	-1413.638968	-1413.204239	-1413.174917	
4a	-1413.605623	-1413.173733	-1413.144003	*i* 265.644
7	-1036.526725	-1036.122058	-1036.097803	
8	-1036.488949	-1036.087035	-1036.063595	*i* 254.482
9	-1036.532881	-1036.127726	-1036.104496	

B3LYP/6-31G (d) level

In conformational study

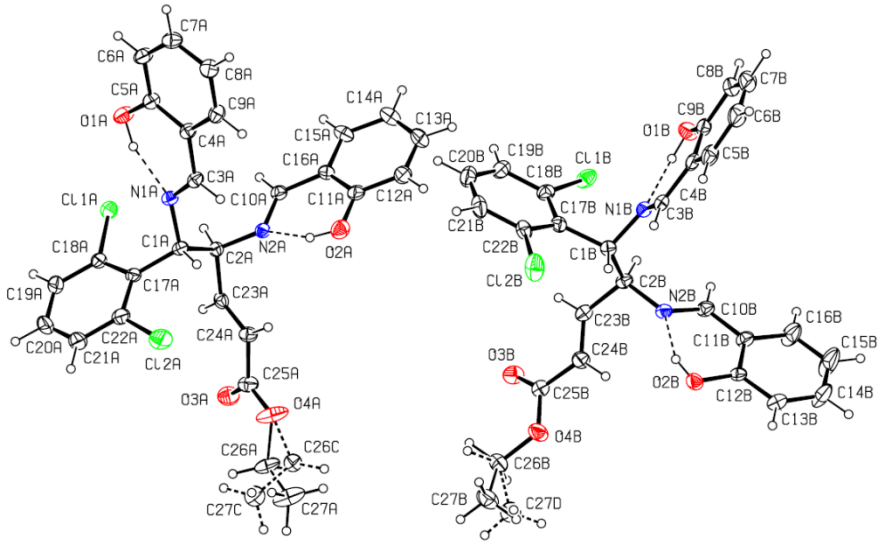
Molecules	Energy (hartree)	E+ZPVE (hartree)	$\Delta H_{0->298.15K}$ (hartree)	$\Delta H_{298.15K}$ (hartree)
10a	-503.066374	-502.8236778	0.253863912	-502.8125101
10b	-503.064069	-502.8214556	0.253811388	-502.8102576
11a	-770.252422	-769.9392989	0.329012264	-769.9234097
11b	-770.247185	-769.9336726	0.329321805	-769.9178632
12a	-770.237393	-769.9235433	0.329627995	-769.907765
12b	-770.239837	-769.9255815	0.329977185	-769.9098598
13a	-314.510961	-314.2835823	0.236500286	-314.2744607
13b	-314.50861	-314.2818954	0.235789335	-314.2728207
14a	-691.627030	-691.3697703	0.270526604	-691.3565034
14b	-691.628181	-691.3707393	0.270710836	-691.3574702
15a	-550.378500	-549.9819231	0.412528699	-549.9659713
15b	-550.346154	-549.9468732	0.414749114	-549.9314049

B3LYP/6-31G (d) level

Appendix D

Crystal data

In Chapter II,



Crystal structure of diimine **3d**

Table S-II-1. Crystal data and structure refinement for d1309.

Identification code	d1309	
Empirical formula	C27 H24 Cl2 N2 O4	
Formula weight	511.38	
Temperature	147(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.5373(8) Å	a= 90°.
	b = 11.2169(8) Å	b= 90°.
	c = 43.787(3) Å	g = 90°.
Volume	5175.5(7) Å ^{3}	
Z	8	
Density (calculated)	1.313 Mg/m^3	
Absorption coefficient	2.548 mm^{-1}	
F(000)	2128	

Crystal size	0.22 x 0.18 x 0.08 mm^3
Theta range for data collection	2.02 to 66.69°.
Index ranges	-12<=h<=12, -8<=k<=13, -50<=l<=52
Reflections collected	33179
Independent reflections	8861 [R(int) = 0.0333]
Completeness to theta = 66.69°	97.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7528 and 0.6640
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8861 / 5 / 662
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0298, wR2 = 0.0753
R indices (all data)	R1 = 0.0308, wR2 = 0.0760
Absolute structure parameter	0.014(8)
Largest diff. peak and hole	0.352 and -0.346 e.$Å^{-3}$

Table S-II-2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for d1309. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1A)	13312(1)	13857(1)	5103(1)	41(1)
Cl(2A)	10963(1)	13921(1)	6215(1)	67(1)
O(1A)	15454(1)	11643(1)	5409(1)	48(1)
O(2A)	9760(1)	9143(1)	5744(1)	47(1)
O(3A)	7667(2)	14464(1)	5392(1)	56(1)
N(1A)	13139(1)	11966(1)	5618(1)	31(1)
N(2A)	10687(1)	10948(1)	5440(1)	29(1)
C(1A)	11927(2)	12592(2)	5647(1)	30(1)
C(2A)	11005(2)	12200(2)	5389(1)	29(1)
C(3A)	13282(2)	11009(2)	5774(1)	32(1)
C(4A)	14446(2)	10325(2)	5768(1)	32(1)
C(5A)	15505(2)	10683(2)	5596(1)	36(1)
C(6A)	16628(2)	10045(2)	5618(1)	44(1)

C(7A)	16691(2)	9042(2)	5801(1)	46(1)
C(8A)	15651(2)	8654(2)	5963(1)	43(1)
C(9A)	14536(2)	9300(2)	5948(1)	38(1)
C(10A)	10980(2)	10216(2)	5229(1)	32(1)
C(11A)	10636(2)	8958(2)	5241(1)	36(1)
C(12A)	9992(2)	8477(2)	5492(1)	40(1)
C(13A)	9577(2)	7304(2)	5480(1)	58(1)
C(14A)	9793(3)	6622(2)	5226(1)	71(1)
C(15A)	10461(3)	7068(2)	4980(1)	67(1)
C(16A)	10878(2)	8233(2)	4988(1)	52(1)
C(17A)	12154(2)	13925(2)	5661(1)	32(1)
C(18A)	12779(2)	14571(2)	5432(1)	37(1)
C(19A)	13007(2)	15779(2)	5453(1)	52(1)
C(20A)	12620(2)	16388(2)	5712(1)	66(1)
C(21A)	11997(2)	15807(2)	5940(1)	60(1)
C(22A)	11768(2)	14601(2)	5913(1)	45(1)
C(23A)	9838(2)	12967(2)	5401(1)	32(1)
C(24A)	8874(2)	12840(2)	5587(1)	36(1)
C(25A)	7804(2)	13693(2)	5580(1)	42(1)
O(4A)	7010(2)	13520(2)	5810(1)	72(1)
C(26A)	6005(4)	14483(5)	5807(1)	56(1)
C(27A)	5297(4)	14308(6)	6093(1)	84(2)
C(26C)	5666(4)	13922(6)	5835(2)	42(2)
C(27C)	5808(7)	15015(6)	6022(2)	55(2)
Cl(1B)	2901(1)	7094(1)	2421(1)	48(1)
Cl(2B)	3251(1)	8325(1)	3625(1)	66(1)
O(1B)	2514(2)	4078(1)	2687(1)	47(1)
O(2B)	-1966(1)	7328(1)	3545(1)	39(1)
O(3B)	318(1)	11453(1)	2770(1)	46(1)
O(4B)	-833(2)	11516(1)	3198(1)	50(1)
N(1B)	1982(1)	5880(1)	3038(1)	31(1)
N(2B)	-482(1)	7195(1)	3081(1)	31(1)
C(1B)	1808(2)	7162(2)	3091(1)	31(1)
C(2B)	632(2)	7605(2)	2912(1)	33(1)
C(3B)	2096(2)	5197(2)	3270(1)	33(1)
C(4B)	2417(2)	3943(2)	3236(1)	36(1)

C(5B)	2637(2)	3440(2)	2949(1)	40(1)
C(6B)	3010(2)	2257(2)	2925(1)	54(1)
C(7B)	3158(2)	1586(2)	3188(1)	66(1)
C(8B)	2931(2)	2056(2)	3471(1)	61(1)
C(9B)	2562(2)	3232(2)	3495(1)	48(1)
C(10B)	-1274(2)	6500(2)	2952(1)	36(1)
C(11B)	-2406(2)	6102(2)	3110(1)	38(1)
C(12B)	-2703(2)	6520(2)	3404(1)	31(1)
C(13B)	-3774(2)	6102(2)	3555(1)	43(1)
C(14B)	-4546(2)	5285(3)	3417(1)	69(1)
C(15B)	-4287(3)	4886(4)	3125(1)	96(1)
C(16B)	-3234(2)	5290(3)	2973(1)	70(1)
C(17B)	3072(2)	7765(2)	3020(1)	33(1)
C(18B)	3638(2)	7769(2)	2733(1)	37(1)
C(19B)	4810(2)	8279(2)	2675(1)	44(1)
C(20B)	5478(2)	8781(2)	2909(1)	52(1)
C(21B)	4989(2)	8783(2)	3200(1)	51(1)
C(22B)	3798(2)	8280(2)	3252(1)	40(1)
C(23B)	593(2)	8940(2)	2885(1)	34(1)
C(24B)	-197(2)	9652(2)	3026(1)	40(1)
C(25B)	-186(2)	10956(2)	2978(1)	35(1)
C(26B)	-831(2)	12799(2)	3192(1)	45(1)
C(27B)	-1065(6)	13295(4)	3498(1)	60(2)
C(27D)	-1820(7)	13164(6)	3421(2)	54(2)

Table S-II-3. Bond lengths [Å] and angles [°] for d1309.

Cl(1A)-C(18A)	1.741(2)
Cl(2A)-C(22A)	1.747(2)
O(1A)-C(5A)	1.355(2)
O(1A)-H(1OA)	0.92(3)
O(2A)-C(12A)	1.355(3)
O(2A)-H(2OA)	0.92(3)
O(3A)-C(25A)	1.203(3)
N(1A)-C(3A)	1.280(2)

N(1A)-C(1A)	1.463(2)
N(2A)-C(10A)	1.276(2)
N(2A)-C(2A)	1.461(2)
C(1A)-C(17A)	1.515(3)
C(1A)-C(2A)	1.554(2)
C(1A)-H(1AA)	1
C(2A)-C(23A)	1.501(2)
C(2A)-H(2AA)	1
C(3A)-C(4A)	1.447(3)
C(3A)-H(3AA)	0.95
C(4A)-C(9A)	1.395(3)
C(4A)-C(5A)	1.407(3)
C(5A)-C(6A)	1.386(3)
C(6A)-C(7A)	1.382(3)
C(6A)-H(6AA)	0.95
C(7A)-C(8A)	1.376(3)
C(7A)-H(7AA)	0.95
C(8A)-C(9A)	1.383(3)
C(8A)-H(8AA)	0.95
C(9A)-H(9AA)	0.95
C(10A)-C(11A)	1.457(3)
C(10A)-H(10A)	0.95
C(11A)-C(16A)	1.398(3)
C(11A)-C(12A)	1.400(3)
C(12A)-C(13A)	1.388(3)
C(13A)-C(14A)	1.367(4)
C(13A)-H(13A)	0.95
C(14A)-C(15A)	1.383(4)
C(14A)-H(14A)	0.95
C(15A)-C(16A)	1.379(3)
C(15A)-H(15A)	0.95
C(16A)-H(16A)	0.95
C(17A)-C(22A)	1.400(3)
C(17A)-C(18A)	1.401(3)
C(18A)-C(19A)	1.379(3)
C(19A)-C(20A)	1.387(4)

C(19A)-H(19A)	0.95
C(20A)-C(21A)	1.361(4)
C(20A)-H(20A)	0.95
C(21A)-C(22A)	1.380(3)
C(21A)-H(21A)	0.95
C(23A)-C(24A)	1.311(3)
C(23A)-H(23A)	0.95
C(24A)-C(25A)	1.479(3)
C(24A)-H(24A)	0.95
C(25A)-O(4A)	1.324(3)
O(4A)-C(26A)	1.513(3)
C(26A)-C(27A)	1.472(5)
C(26A)-H(26A)	0.99
C(26A)-H(26B)	0.99
C(27A)-H(27A)	0.98
C(27A)-H(27B)	0.98
C(27A)-H(27C)	0.98
C(26C)-C(27C)	1.482(5)
C(26C)-H(26C)	0.99
C(26C)-H(26D)	0.99
C(27C)-H(27D)	0.98
C(27C)-H(27E)	0.98
C(27C)-H(27F)	0.98
Cl(1B)-C(18B)	1.742(2)
Cl(2B)-C(22B)	1.734(2)
O(1B)-C(5B)	1.357(2)
O(1B)-H(1OB)	0.88(3)
O(2B)-C(12B)	1.344(2)
O(2B)-H(2OB)	0.87(3)
O(3B)-C(25B)	1.195(2)
O(4B)-C(25B)	1.335(2)
O(4B)-C(26B)	1.440(2)
N(1B)-C(3B)	1.277(2)
N(1B)-C(1B)	1.468(2)
N(2B)-C(10B)	1.274(2)
N(2B)-C(2B)	1.460(2)

C(1B)-C(17B)	1.525(3)
C(1B)-C(2B)	1.548(2)
C(1B)-H(1BA)	1
C(2B)-C(23B)	1.503(3)
C(2B)-H(2BA)	1
C(3B)-C(4B)	1.454(3)
C(3B)-H(3BA)	0.95
C(4B)-C(9B)	1.396(3)
C(4B)-C(5B)	1.398(3)
C(5B)-C(6B)	1.388(3)
C(6B)-C(7B)	1.384(4)
C(6B)-H(6BA)	0.95
C(7B)-C(8B)	1.369(4)
C(7B)-H(7BA)	0.95
C(8B)-C(9B)	1.379(4)
C(8B)-H(8BA)	0.95
C(9B)-H(9BA)	0.95
C(10B)-C(11B)	1.449(3)
C(10B)-H(10B)	0.95
C(11B)-C(16B)	1.396(3)
C(11B)-C(12B)	1.405(2)
C(12B)-C(13B)	1.391(3)
C(13B)-C(14B)	1.367(3)
C(13B)-H(13B)	0.95
C(14B)-C(15B)	1.382(4)
C(14B)-H(14B)	0.95
C(15B)-C(16B)	1.372(4)
C(15B)-H(15B)	0.95
C(16B)-H(16B)	0.95
C(17B)-C(18B)	1.392(3)
C(17B)-C(22B)	1.395(3)
C(18B)-C(19B)	1.384(3)
C(19B)-C(20B)	1.363(3)
C(19B)-H(19B)	0.95
C(20B)-C(21B)	1.373(3)
C(20B)-H(20B)	0.95

C(21B)-C(22B)	1.394(3)
C(21B)-H(21B)	0.95
C(23B)-C(24B)	1.308(3)
C(23B)-H(23B)	0.95
C(24B)-C(25B)	1.478(3)
C(24B)-H(24B)	0.95
C(26B)-C(27B)	1.472(4)
C(26B)-H(26E)	0.99
C(26B)-H(26F)	0.99
C(27B)-H(27G)	0.98
C(27B)-H(27H)	0.98
C(27B)-H(27I)	0.98
C(27D)-H(27J)	0.98
C(27D)-H(27K)	0.98
C(27D)-H(27L)	0.98
C(5A)-O(1A)-H(1OA)	103.9(18)
C(12A)-O(2A)-H(2OA)	106.6(17)
C(3A)-N(1A)-C(1A)	117.28(15)
C(10A)-N(2A)-C(2A)	116.88(15)
N(1A)-C(1A)-C(17A)	109.85(15)
N(1A)-C(1A)-C(2A)	110.24(13)
C(17A)-C(1A)-C(2A)	114.04(14)
N(1A)-C(1A)-H(1AA)	107.5
C(17A)-C(1A)-H(1AA)	107.5
C(2A)-C(1A)-H(1AA)	107.5
N(2A)-C(2A)-C(23A)	110.97(14)
N(2A)-C(2A)-C(1A)	107.67(14)
C(23A)-C(2A)-C(1A)	108.96(13)
N(2A)-C(2A)-H(2AA)	109.7
C(23A)-C(2A)-H(2AA)	109.7
C(1A)-C(2A)-H(2AA)	109.7
N(1A)-C(3A)-C(4A)	122.40(16)
N(1A)-C(3A)-H(3AA)	118.8
C(4A)-C(3A)-H(3AA)	118.8
C(9A)-C(4A)-C(5A)	118.88(17)
C(9A)-C(4A)-C(3A)	119.10(17)

C(5A)-C(4A)-C(3A)	121.99(17)
O(1A)-C(5A)-C(6A)	119.14(17)
O(1A)-C(5A)-C(4A)	121.36(17)
C(6A)-C(5A)-C(4A)	119.50(18)
C(7A)-C(6A)-C(5A)	120.14(19)
C(7A)-C(6A)-H(6AA)	119.9
C(5A)-C(6A)-H(6AA)	119.9
C(8A)-C(7A)-C(6A)	121.19(19)
C(8A)-C(7A)-H(7AA)	119.4
C(6A)-C(7A)-H(7AA)	119.4
C(7A)-C(8A)-C(9A)	119.06(18)
C(7A)-C(8A)-H(8AA)	120.5
C(9A)-C(8A)-H(8AA)	120.5
C(8A)-C(9A)-C(4A)	121.16(18)
C(8A)-C(9A)-H(9AA)	119.4
C(4A)-C(9A)-H(9AA)	119.4
N(2A)-C(10A)-C(11A)	122.48(17)
N(2A)-C(10A)-H(10A)	118.8
C(11A)-C(10A)-H(10A)	118.8
C(16A)-C(11A)-C(12A)	119.11(19)
C(16A)-C(11A)-C(10A)	119.27(18)
C(12A)-C(11A)-C(10A)	121.48(17)
O(2A)-C(12A)-C(13A)	119.8(2)
O(2A)-C(12A)-C(11A)	120.96(18)
C(13A)-C(12A)-C(11A)	119.3(2)
C(14A)-C(13A)-C(12A)	120.6(2)
C(14A)-C(13A)-H(13A)	119.7
C(12A)-C(13A)-H(13A)	119.7
C(13A)-C(14A)-C(15A)	121.1(2)
C(13A)-C(14A)-H(14A)	119.5
C(15A)-C(14A)-H(14A)	119.5
C(16A)-C(15A)-C(14A)	119.1(2)
C(16A)-C(15A)-H(15A)	120.5
C(14A)-C(15A)-H(15A)	120.5
C(15A)-C(16A)-C(11A)	120.8(2)
C(15A)-C(16A)-H(16A)	119.6

C(11A)-C(16A)-H(16A)	119.6
C(22A)-C(17A)-C(18A)	114.87(18)
C(22A)-C(17A)-C(1A)	121.35(18)
C(18A)-C(17A)-C(1A)	123.76(15)
C(19A)-C(18A)-C(17A)	122.90(19)
C(19A)-C(18A)-Cl(1A)	116.75(17)
C(17A)-C(18A)-Cl(1A)	120.35(14)
C(18A)-C(19A)-C(20A)	119.1(2)
C(18A)-C(19A)-H(19A)	120.4
C(20A)-C(19A)-H(19A)	120.4
C(21A)-C(20A)-C(19A)	120.4(2)
C(21A)-C(20A)-H(20A)	119.8
C(19A)-C(20A)-H(20A)	119.8
C(20A)-C(21A)-C(22A)	119.5(2)
C(20A)-C(21A)-H(21A)	120.3
C(22A)-C(21A)-H(21A)	120.3
C(21A)-C(22A)-C(17A)	123.2(2)
C(21A)-C(22A)-Cl(2A)	116.68(17)
C(17A)-C(22A)-Cl(2A)	120.13(17)
C(24A)-C(23A)-C(2A)	126.43(17)
C(24A)-C(23A)-H(23A)	116.8
C(2A)-C(23A)-H(23A)	116.8
C(23A)-C(24A)-C(25A)	120.61(18)
C(23A)-C(24A)-H(24A)	119.7
C(25A)-C(24A)-H(24A)	119.7
O(3A)-C(25A)-O(4A)	123.38(19)
O(3A)-C(25A)-C(24A)	124.72(19)
O(4A)-C(25A)-C(24A)	111.90(18)
C(25A)-O(4A)-C(26A)	109.2(2)
C(27A)-C(26A)-O(4A)	104.4(3)
C(27A)-C(26A)-H(26A)	110.9
O(4A)-C(26A)-H(26A)	110.9
C(27A)-C(26A)-H(26B)	110.9
O(4A)-C(26A)-H(26B)	110.9
H(26A)-C(26A)-H(26B)	108.9
C(26A)-C(27A)-H(27A)	109.5

C(26A)-C(27A)-H(27B)	109.5
H(27A)-C(27A)-H(27B)	109.5
C(26A)-C(27A)-H(27C)	109.5
H(27A)-C(27A)-H(27C)	109.5
H(27B)-C(27A)-H(27C)	109.5
C(27C)-C(26C)-H(26C)	111.5
C(27C)-C(26C)-H(26D)	111.5
H(26C)-C(26C)-H(26D)	109.4
C(26C)-C(27C)-H(27D)	109.5
C(26C)-C(27C)-H(27E)	109.5
H(27D)-C(27C)-H(27E)	109.5
C(26C)-C(27C)-H(27F)	109.5
H(27D)-C(27C)-H(27F)	109.5
H(27E)-C(27C)-H(27F)	109.5
C(5B)-O(1B)-H(1OB)	107.8(16)
C(12B)-O(2B)-H(2OB)	107.0(16)
C(25B)-O(4B)-C(26B)	117.03(16)
C(3B)-N(1B)-C(1B)	118.30(15)
C(10B)-N(2B)-C(2B)	119.70(15)
N(1B)-C(1B)-C(17B)	107.05(14)
N(1B)-C(1B)-C(2B)	109.60(14)
C(17B)-C(1B)-C(2B)	117.02(14)
N(1B)-C(1B)-H(1BA)	107.6
C(17B)-C(1B)-H(1BA)	107.6
C(2B)-C(1B)-H(1BA)	107.6
N(2B)-C(2B)-C(23B)	109.42(15)
N(2B)-C(2B)-C(1B)	106.69(13)
C(23B)-C(2B)-C(1B)	112.43(15)
N(2B)-C(2B)-H(2BA)	109.4
C(23B)-C(2B)-H(2BA)	109.4
C(1B)-C(2B)-H(2BA)	109.4
N(1B)-C(3B)-C(4B)	121.35(17)
N(1B)-C(3B)-H(3BA)	119.3
C(4B)-C(3B)-H(3BA)	119.3
C(9B)-C(4B)-C(5B)	118.84(19)
C(9B)-C(4B)-C(3B)	119.69(18)

C(5B)-C(4B)-C(3B)	121.41(17)
O(1B)-C(5B)-C(6B)	117.9(2)
O(1B)-C(5B)-C(4B)	122.07(18)
C(6B)-C(5B)-C(4B)	120.06(19)
C(7B)-C(6B)-C(5B)	119.3(2)
C(7B)-C(6B)-H(6BA)	120.3
C(5B)-C(6B)-H(6BA)	120.3
C(8B)-C(7B)-C(6B)	121.6(2)
C(8B)-C(7B)-H(7BA)	119.2
C(6B)-C(7B)-H(7BA)	119.2
C(7B)-C(8B)-C(9B)	119.2(2)
C(7B)-C(8B)-H(8BA)	120.4
C(9B)-C(8B)-H(8BA)	120.4
C(8B)-C(9B)-C(4B)	121.0(2)
C(8B)-C(9B)-H(9BA)	119.5
C(4B)-C(9B)-H(9BA)	119.5
N(2B)-C(10B)-C(11B)	121.05(16)
N(2B)-C(10B)-H(10B)	119.5
C(11B)-C(10B)-H(10B)	119.5
C(16B)-C(11B)-C(12B)	118.15(19)
C(16B)-C(11B)-C(10B)	120.65(18)
C(12B)-C(11B)-C(10B)	121.19(17)
O(2B)-C(12B)-C(13B)	118.47(16)
O(2B)-C(12B)-C(11B)	121.14(17)
C(13B)-C(12B)-C(11B)	120.38(18)
C(14B)-C(13B)-C(12B)	119.82(19)
C(14B)-C(13B)-H(13B)	120.1
C(12B)-C(13B)-H(13B)	120.1
C(13B)-C(14B)-C(15B)	120.6(2)
C(13B)-C(14B)-H(14B)	119.7
C(15B)-C(14B)-H(14B)	119.7
C(16B)-C(15B)-C(14B)	120.2(2)
C(16B)-C(15B)-H(15B)	119.9
C(14B)-C(15B)-H(15B)	119.9
C(15B)-C(16B)-C(11B)	120.8(2)
C(15B)-C(16B)-H(16B)	119.6

C(11B)-C(16B)-H(16B)	119.6
C(18B)-C(17B)-C(22B)	114.83(18)
C(18B)-C(17B)-C(1B)	123.99(16)
C(22B)-C(17B)-C(1B)	120.99(16)
C(19B)-C(18B)-C(17B)	123.22(19)
C(19B)-C(18B)-Cl(1B)	115.80(15)
C(17B)-C(18B)-Cl(1B)	120.97(15)
C(20B)-C(19B)-C(18B)	119.7(2)
C(20B)-C(19B)-H(19B)	120.2
C(18B)-C(19B)-H(19B)	120.2
C(19B)-C(20B)-C(21B)	120.2(2)
C(19B)-C(20B)-H(20B)	119.9
C(21B)-C(20B)-H(20B)	119.9
C(20B)-C(21B)-C(22B)	119.2(2)
C(20B)-C(21B)-H(21B)	120.4
C(22B)-C(21B)-H(21B)	120.4
C(21B)-C(22B)-C(17B)	122.86(19)
C(21B)-C(22B)-Cl(2B)	116.18(16)
C(17B)-C(22B)-Cl(2B)	120.96(16)
C(24B)-C(23B)-C(2B)	126.00(18)
C(24B)-C(23B)-H(23B)	117
C(2B)-C(23B)-H(23B)	117
C(23B)-C(24B)-C(25B)	122.17(18)
C(23B)-C(24B)-H(24B)	118.9
C(25B)-C(24B)-H(24B)	118.9
O(3B)-C(25B)-O(4B)	123.97(18)
O(3B)-C(25B)-C(24B)	124.97(17)
O(4B)-C(25B)-C(24B)	111.06(16)
O(4B)-C(26B)-C(27B)	111.1(2)
O(4B)-C(26B)-H(26E)	109.4
C(27B)-C(26B)-H(26E)	109.4
O(4B)-C(26B)-H(26F)	109.4
C(27B)-C(26B)-H(26F)	109.4
H(26E)-C(26B)-H(26F)	108
C(26B)-C(27B)-H(27G)	109.5
C(26B)-C(27B)-H(27H)	109.5

H(27G)-C(27B)-H(27H)	109.5
C(26B)-C(27B)-H(27I)	109.5
H(27G)-C(27B)-H(27I)	109.5
H(27H)-C(27B)-H(27I)	109.5
H(27J)-C(27D)-H(27K)	109.5
H(27J)-C(27D)-H(27L)	109.5
H(27K)-C(27D)-H(27L)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S-II-4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for d1309. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1A)	40(1)	40(1)	41(1)	2(1)	7(1)	-3(1)
Cl(2A)	69(1)	83(1)	48(1)	-31(1)	19(1)	-6(1)
O(1A)	37(1)	50(1)	56(1)	18(1)	13(1)	10(1)
O(2A)	43(1)	48(1)	49(1)	10(1)	6(1)	0(1)
O(3A)	43(1)	52(1)	73(1)	6(1)	-12(1)	15(1)
N(1A)	26(1)	38(1)	29(1)	-4(1)	-1(1)	4(1)
N(2A)	25(1)	31(1)	31(1)	-2(1)	-3(1)	1(1)
C(1A)	25(1)	37(1)	30(1)	-4(1)	1(1)	3(1)
C(2A)	27(1)	30(1)	29(1)	-4(1)	0(1)	-2(1)
C(3A)	27(1)	41(1)	27(1)	-2(1)	-1(1)	-1(1)
C(4A)	27(1)	39(1)	29(1)	-1(1)	-3(1)	1(1)
C(5A)	33(1)	39(1)	36(1)	3(1)	1(1)	2(1)
C(6A)	31(1)	49(1)	53(1)	6(1)	7(1)	7(1)
C(7A)	35(1)	47(1)	55(1)	3(1)	-5(1)	12(1)
C(8A)	42(1)	42(1)	44(1)	8(1)	-7(1)	4(1)
C(9A)	33(1)	44(1)	36(1)	4(1)	-3(1)	-3(1)
C(10A)	28(1)	34(1)	36(1)	0(1)	0(1)	3(1)
C(11A)	30(1)	29(1)	49(1)	0(1)	-1(1)	6(1)
C(12A)	26(1)	35(1)	58(1)	5(1)	0(1)	8(1)

C(13A)	42(1)	32(1)	99(2)	13(1)	12(1)	4(1)
C(14A)	60(2)	26(1)	126(2)	-4(1)	7(2)	3(1)
C(15A)	69(2)	37(1)	95(2)	-18(1)	9(1)	7(1)
C(16A)	56(1)	33(1)	66(1)	-10(1)	9(1)	8(1)
C(17A)	21(1)	36(1)	39(1)	-13(1)	-6(1)	2(1)
C(18A)	24(1)	36(1)	51(1)	-9(1)	-5(1)	2(1)
C(19A)	34(1)	38(1)	84(2)	-7(1)	-2(1)	-4(1)
C(20A)	45(1)	40(1)	111(2)	-32(1)	-6(1)	-4(1)
C(21A)	43(1)	58(2)	80(2)	-40(1)	1(1)	-5(1)
C(22A)	30(1)	57(1)	48(1)	-24(1)	-1(1)	-1(1)
C(23A)	32(1)	27(1)	36(1)	-2(1)	-9(1)	-1(1)
C(24A)	34(1)	39(1)	34(1)	-1(1)	-3(1)	8(1)
C(25A)	34(1)	54(1)	38(1)	-13(1)	-10(1)	10(1)
O(4A)	45(1)	129(2)	40(1)	-2(1)	2(1)	44(1)
C(26A)	31(2)	84(3)	52(2)	0(2)	0(2)	23(2)
C(27A)	49(3)	136(5)	65(3)	3(3)	10(2)	35(3)
O(4C)	45(1)	129(2)	40(1)	-2(1)	2(1)	44(1)
Cl(1B)	38(1)	71(1)	34(1)	-2(1)	6(1)	-2(1)
Cl(2B)	80(1)	79(1)	37(1)	-8(1)	-8(1)	-31(1)
O(1B)	58(1)	38(1)	44(1)	-3(1)	7(1)	3(1)
O(2B)	48(1)	35(1)	34(1)	-7(1)	10(1)	-3(1)
O(3B)	54(1)	48(1)	36(1)	11(1)	9(1)	8(1)
O(4B)	67(1)	36(1)	46(1)	-3(1)	21(1)	1(1)
N(1B)	28(1)	33(1)	32(1)	2(1)	0(1)	0(1)
N(2B)	29(1)	35(1)	30(1)	-3(1)	2(1)	3(1)
C(1B)	33(1)	33(1)	28(1)	0(1)	0(1)	0(1)
C(2B)	30(1)	40(1)	28(1)	-2(1)	2(1)	3(1)
C(3B)	25(1)	38(1)	36(1)	4(1)	3(1)	-5(1)
C(4B)	24(1)	36(1)	48(1)	7(1)	1(1)	-7(1)
C(5B)	31(1)	34(1)	55(1)	6(1)	4(1)	-4(1)
C(6B)	47(1)	36(1)	80(2)	-2(1)	9(1)	-4(1)
C(7B)	53(1)	33(1)	110(2)	21(1)	4(1)	-1(1)
C(8B)	52(1)	50(1)	81(2)	29(1)	0(1)	-6(1)
C(9B)	40(1)	50(1)	55(1)	20(1)	0(1)	-7(1)
C(10B)	31(1)	46(1)	31(1)	-8(1)	0(1)	3(1)
C(11B)	28(1)	48(1)	37(1)	-7(1)	-1(1)	3(1)

C(12B)	26(1)	33(1)	34(1)	-1(1)	-1(1)	8(1)
C(13B)	33(1)	55(1)	42(1)	1(1)	5(1)	7(1)
C(14B)	33(1)	105(2)	68(2)	-8(2)	10(1)	-22(1)
C(15B)	54(2)	152(3)	80(2)	-47(2)	10(2)	-53(2)
C(16B)	43(1)	108(2)	57(1)	-38(1)	3(1)	-26(1)
C(17B)	33(1)	26(1)	39(1)	6(1)	-5(1)	3(1)
C(18B)	32(1)	39(1)	42(1)	6(1)	0(1)	6(1)
C(19B)	33(1)	44(1)	54(1)	12(1)	5(1)	2(1)
C(20B)	40(1)	44(1)	71(1)	13(1)	-1(1)	-7(1)
C(21B)	51(1)	37(1)	66(1)	2(1)	-20(1)	-12(1)
C(22B)	46(1)	30(1)	43(1)	4(1)	-9(1)	-3(1)
C(23B)	30(1)	43(1)	27(1)	5(1)	0(1)	1(1)
C(24B)	47(1)	39(1)	35(1)	0(1)	9(1)	-1(1)
C(25B)	34(1)	42(1)	30(1)	0(1)	-2(1)	1(1)
C(26B)	52(1)	37(1)	48(1)	-5(1)	-5(1)	1(1)
C(27B)	83(4)	44(2)	54(2)	-10(2)	11(2)	3(2)
C(26D)	52(1)	37(1)	48(1)	-5(1)	-5(1)	1(1)

Table S-II-5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å ^{2}x 10 ^{3}) for d1309.

	x	y	z	U(eq)
H(1AA)	11539	12347	5846	36
H(2AA)	11429	12291	5186	35
H(3AA)	12599	10739	5897	38
H(6AA)	17356	10299	5508	53
H(7AA)	17466	8612	5815	55
H(8AA)	15700	7952	6084	51
H(9AA)	13818	9041	6061	46
H(10A)	11440	10500	5057	39
H(13A)	9139	6972	5649	69
H(14A)	9479	5828	5220	85
H(15A)	10630	6579	4807	80
H(16A)	11336	8547	4819	62
H(19A)	13423	16188	5291	62

H(20A)	12793	17216	5731	79
H(21A)	11721	16229	6116	73
H(23A)	9795	13607	5259	38
H(24A)	8862	12193	5727	43
H(26A)	6397	15285	5800	67
H(26B)	5439	14392	5628	67
H(27A)	4634	14916	6110	125
H(27B)	5880	14376	6267	125
H(27C)	4908	13515	6093	125
H(26C)	5300	14103	5632	50
H(26D)	5131	13321	5939	50
H(27D)	4977	15390	6050	83
H(27E)	6381	15572	5918	83
H(27F)	6162	14804	6222	83
H(1BA)	1632	7277	3313	37
H(2BA)	630	7243	2703	39
H(3BA)	1969	5515	3469	40
H(6BA)	3161	1912	2730	65
H(7BA)	3425	779	3171	79
H(8BA)	3026	1578	3648	73
H(9BA)	2404	3562	3691	58
H(10B)	-1121	6238	2749	43
H(13B)	-3967	6382	3755	52
H(14B)	-5268	4989	3523	82
H(15B)	-4839	4330	3030	115
H(16B)	-3065	5014	2772	83
H(19B)	5148	8279	2474	53
H(20B)	6283	9131	2870	62
H(21B)	5456	9123	3363	62
H(23B)	1198	9301	2753	40
H(24B)	-797	9319	3164	48
H(26E)	-1495	13083	3049	55
H(26F)	0	13085	3115	55
H(27G)	-1058	14167	3487	91
H(27H)	-400	13024	3638	91
H(27I)	-1894	13022	3572	91

H(26G)	-1051	13096	2985	55
H(26H)	13	13115	3249	55
H(27J)	-1871	14036	3429	81
H(27K)	-1588	12856	3623	81
H(27L)	-2646	12838	3361	81
H(1OA)	14660(30)	11960(30)	5445(6)	75(8)
H(2OA)	10050(30)	9900(30)	5702(6)	72(9)
H(1OB)	2260(30)	4800(20)	2737(6)	59(7)
H(2OB)	-1300(20)	7420(20)	3432(5)	50(7)

Table S-II-6. Torsion angles [°] for d1309.

C(3A)-N(1A)-C(1A)-C(17A)	138.98(15)
C(3A)-N(1A)-C(1A)-C(2A)	-94.52(17)
C(10A)-N(2A)-C(2A)-C(23A)	121.07(16)
C(10A)-N(2A)-C(2A)-C(1A)	-119.76(16)
N(1A)-C(1A)-C(2A)-N(2A)	66.73(17)
C(17A)-C(1A)-C(2A)-N(2A)	-169.16(14)
N(1A)-C(1A)-C(2A)-C(23A)	-172.84(14)
C(17A)-C(1A)-C(2A)-C(23A)	-48.73(19)
C(1A)-N(1A)-C(3A)-C(4A)	-178.76(15)
N(1A)-C(3A)-C(4A)-C(9A)	179.24(17)
N(1A)-C(3A)-C(4A)-C(5A)	1.3(3)
C(9A)-C(4A)-C(5A)-O(1A)	177.24(17)
C(3A)-C(4A)-C(5A)-O(1A)	-4.9(3)
C(9A)-C(4A)-C(5A)-C(6A)	-3.0(3)
C(3A)-C(4A)-C(5A)-C(6A)	174.92(17)
O(1A)-C(5A)-C(6A)-C(7A)	-178.00(19)
C(4A)-C(5A)-C(6A)-C(7A)	2.2(3)
C(5A)-C(6A)-C(7A)-C(8A)	0.0(3)
C(6A)-C(7A)-C(8A)-C(9A)	-1.5(3)
C(7A)-C(8A)-C(9A)-C(4A)	0.7(3)
C(5A)-C(4A)-C(9A)-C(8A)	1.6(3)

C(3A)-C(4A)-C(9A)-C(8A)	-176.40(18)
C(2A)-N(2A)-C(10A)-C(11A)	-175.45(16)
N(2A)-C(10A)-C(11A)-C(16A)	173.75(19)
N(2A)-C(10A)-C(11A)-C(12A)	-1.9(3)
C(16A)-C(11A)-C(12A)-O(2A)	178.72(19)
C(10A)-C(11A)-C(12A)-O(2A)	-5.6(3)
C(16A)-C(11A)-C(12A)-C(13A)	-1.9(3)
C(10A)-C(11A)-C(12A)-C(13A)	173.81(19)
O(2A)-C(12A)-C(13A)-C(14A)	179.4(2)
C(11A)-C(12A)-C(13A)-C(14A)	0.0(3)
C(12A)-C(13A)-C(14A)-C(15A)	2.0(4)
C(13A)-C(14A)-C(15A)-C(16A)	-2.0(4)
C(14A)-C(15A)-C(16A)-C(11A)	0.1(4)
C(12A)-C(11A)-C(16A)-C(15A)	1.8(3)
C(10A)-C(11A)-C(16A)-C(15A)	-174.0(2)
N(1A)-C(1A)-C(17A)-C(22A)	-120.34(18)
C(2A)-C(1A)-C(17A)-C(22A)	115.34(19)
N(1A)-C(1A)-C(17A)-C(18A)	58.1(2)
C(2A)-C(1A)-C(17A)-C(18A)	-66.2(2)
C(22A)-C(17A)-C(18A)-C(19A)	0.3(3)
C(1A)-C(17A)-C(18A)-C(19A)	-178.21(18)
C(22A)-C(17A)-C(18A)-Cl(1A)	-179.76(14)
C(1A)-C(17A)-C(18A)-Cl(1A)	1.7(2)
C(17A)-C(18A)-C(19A)-C(20A)	1.0(3)
Cl(1A)-C(18A)-C(19A)-C(20A)	-178.97(17)
C(18A)-C(19A)-C(20A)-C(21A)	-1.6(4)
C(19A)-C(20A)-C(21A)-C(22A)	1.0(4)
C(20A)-C(21A)-C(22A)-C(17A)	0.3(4)
C(20A)-C(21A)-C(22A)-Cl(2A)	179.97(19)
C(18A)-C(17A)-C(22A)-C(21A)	-1.0(3)
C(1A)-C(17A)-C(22A)-C(21A)	177.6(2)
C(18A)-C(17A)-C(22A)-Cl(2A)	179.40(14)
C(1A)-C(17A)-C(22A)-Cl(2A)	-2.0(3)
N(2A)-C(2A)-C(23A)-C(24A)	38.2(2)
C(1A)-C(2A)-C(23A)-C(24A)	-80.2(2)
C(2A)-C(23A)-C(24A)-C(25A)	177.65(16)

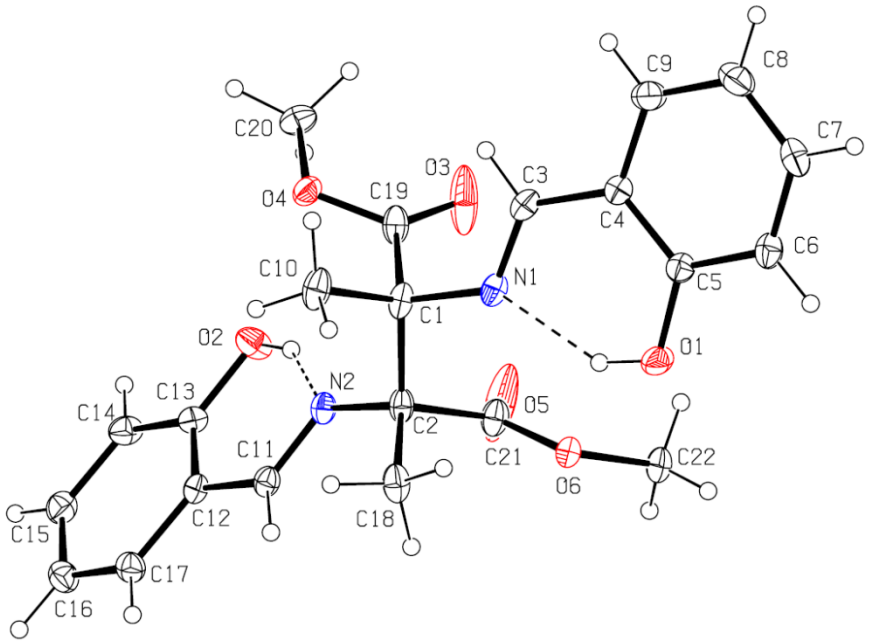
C(23A)-C(24A)-C(25A)-O(3A)	7.9(3)
C(23A)-C(24A)-C(25A)-O(4A)	-171.34(19)

Table S-II-7. Hydrogen bonds for d1309 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1A)-H(1OA)...N(1A)	0.92(3)	1.78(3)	2.630(2)	153(3)
O(2A)-H(2OA)...N(2A)	0.92(3)	1.77(3)	2.612(2)	150(3)
O(1B)-H(1OB)...N(1B)	0.88(3)	1.81(3)	2.601(2)	147(2)
O(2B)-H(2OB)...N(2B)	0.87(3)	1.78(2)	2.5682(19)	150(2)

Symmetry transformations used to generate equivalent atoms:

In Chapter III,



Crystal structure of diimine **3**

Table S-III-1. Crystal data and structure refinement for d12336.

Identification code	d12336	
Empirical formula	C22 H24 N2 O6	
Formula weight	412.43	
Temperature	147(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 6.9679(3) Å	α= 90°.
	b = 19.0540(9) Å	β= 93.428(2)°.
	c = 7.6683(4) Å	γ = 90°.
Volume	1016.27(8) Å^3	

Z	2
Density (calculated)	1.348 Mg/m^3
Absorption coefficient	0.819 mm^{-1}
F(000)	436
Crystal size	0.28 x 0.15 x 0.12 mm^3
Theta range for data collection	4.64 to 66.31°.
Index ranges	-8<=h<=7, -22<=k<=21, -9<=l<=9
Reflections collected	12698
Independent reflections	3412 [R(int) = 0.0305]
Completeness to theta = 66.31°	97.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7528 and 0.6930
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3412 / 1 / 283
Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R1 = 0.0305, wR2 = 0.0761
R indices (all data)	R1 = 0.0306, wR2 = 0.0763
Absolute structure parameter	0.16(14)
Largest diff. peak and hole	0.175 and -0.217 e.$Å^{-3}$

Table S-III-2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for d12336. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4456(2)	3221(1)	5202(2)	38(1)
O(2)	6771(2)	6630(1)	10659(2)	37(1)
O(3)	3030(3)	5554(1)	7322(3)	78(1)
O(4)	4970(2)	6389(1)	6500(2)	31(1)
O(5)	5173(3)	4783(1)	10189(3)	90(1)
O(6)	5861(2)	3857(1)	8609(1)	26(1)
N(1)	5003(2)	4582(1)	5374(2)	27(1)
N(2)	7816(2)	5568(1)	8809(2)	26(1)
C(1)	5994(3)	5204(1)	6119(2)	29(1)
C(2)	7246(2)	4944(1)	7780(2)	27(1)

C(3)	3520(2)	4655(1)	4325(2)	29(1)
C(4)	2443(2)	4058(1)	3611(2)	26(1)
C(5)	2954(2)	3367(1)	4058(2)	27(1)
C(6)	1909(3)	2804(1)	3314(2)	34(1)
C(7)	364(2)	2932(1)	2158(2)	36(1)
C(8)	-206(3)	3611(1)	1750(2)	43(1)
C(9)	831(3)	4167(1)	2467(2)	37(1)
C(10)	7250(3)	5531(1)	4761(2)	38(1)
C(11)	9532(2)	5640(1)	9476(2)	26(1)
C(12)	10041(2)	6224(1)	10648(2)	24(1)
C(13)	8639(2)	6690(1)	11209(2)	27(1)
C(14)	9173(3)	7231(1)	12369(2)	32(1)
C(15)	11075(3)	7311(1)	12937(2)	33(1)
C(16)	12483(2)	6854(1)	12409(2)	33(1)
C(17)	11965(2)	6313(1)	11279(2)	30(1)
C(18)	8899(2)	4481(1)	7228(2)	34(1)
C(19)	4482(3)	5728(1)	6719(2)	32(1)
C(20)	3600(3)	6904(1)	7062(2)	36(1)
C(21)	5945(2)	4536(1)	8996(2)	32(1)
C(22)	4659(2)	3434(1)	9666(2)	34(1)

Table S-III-3. Bond lengths [Å] and angles [°] for d12336.

O(1)-C(5)	1.354(2)
O(1)-H(1O)	0.86(4)
O(2)-C(13)	1.349(2)
O(2)-H(2O)	0.86(3)
O(3)-C(19)	1.184(2)
O(4)-C(19)	1.318(2)
O(4)-C(20)	1.453(2)
O(5)-C(21)	1.186(2)
O(6)-C(21)	1.327(2)
O(6)-C(22)	1.4450(19)
N(1)-C(3)	1.278(2)
N(1)-C(1)	1.470(2)

N(2)-C(11)	1.280(2)
N(2)-C(2)	1.467(2)
C(1)-C(10)	1.533(2)
C(1)-C(19)	1.542(2)
C(1)-C(2)	1.579(2)
C(2)-C(18)	1.532(2)
C(2)-C(21)	1.549(2)
C(3)-C(4)	1.453(2)
C(3)-H(3A)	0.95
C(4)-C(9)	1.399(2)
C(4)-C(5)	1.401(2)
C(5)-C(6)	1.398(2)
C(6)-C(7)	1.375(3)
C(6)-H(6A)	0.95
C(7)-C(8)	1.384(3)
C(7)-H(7A)	0.95
C(8)-C(9)	1.379(3)
C(8)-H(8A)	0.95
C(9)-H(9A)	0.95
C(10)-H(10A)	0.98
C(10)-H(10B)	0.98
C(10)-H(10C)	0.98
C(11)-C(12)	1.461(2)
C(11)-H(11A)	0.95
C(12)-C(13)	1.407(2)
C(12)-C(17)	1.408(2)
C(13)-C(14)	1.398(2)
C(14)-C(15)	1.379(2)
C(14)-H(14A)	0.95
C(15)-C(16)	1.389(3)
C(15)-H(15A)	0.95
C(16)-C(17)	1.382(2)
C(16)-H(16A)	0.95
C(17)-H(17A)	0.95
C(18)-H(18A)	0.98
C(18)-H(18B)	0.98

C(18)-H(18C)	0.98
C(20)-H(20A)	0.98
C(20)-H(20B)	0.98
C(20)-H(20C)	0.98
C(22)-H(22A)	0.98
C(22)-H(22B)	0.98
C(22)-H(22C)	0.98
C(5)-O(1)-H(1O)	109(2)
C(13)-O(2)-H(2O)	106.0(15)
C(19)-O(4)-C(20)	115.38(13)
C(21)-O(6)-C(22)	115.92(12)
C(3)-N(1)-C(1)	119.96(14)
C(11)-N(2)-C(2)	121.19(14)
N(1)-C(1)-C(10)	109.79(13)
N(1)-C(1)-C(19)	108.96(13)
C(10)-C(1)-C(19)	111.52(14)
N(1)-C(1)-C(2)	106.61(12)
C(10)-C(1)-C(2)	111.38(14)
C(19)-C(1)-C(2)	108.43(12)
N(2)-C(2)-C(18)	115.59(13)
N(2)-C(2)-C(21)	103.43(12)
C(18)-C(2)-C(21)	110.69(13)
N(2)-C(2)-C(1)	107.43(12)
C(18)-C(2)-C(1)	110.23(13)
C(21)-C(2)-C(1)	109.13(13)
N(1)-C(3)-C(4)	122.07(14)
N(1)-C(3)-H(3A)	119
C(4)-C(3)-H(3A)	119
C(9)-C(4)-C(5)	118.44(15)
C(9)-C(4)-C(3)	119.79(15)
C(5)-C(4)-C(3)	121.76(14)
O(1)-C(5)-C(6)	118.04(15)
O(1)-C(5)-C(4)	121.78(14)
C(6)-C(5)-C(4)	120.18(14)
C(7)-C(6)-C(5)	119.70(17)
C(7)-C(6)-H(6A)	120.1

C(5)-C(6)-H(6A)	120.1
C(6)-C(7)-C(8)	120.97(17)
C(6)-C(7)-H(7A)	119.5
C(8)-C(7)-H(7A)	119.5
C(9)-C(8)-C(7)	119.50(16)
C(9)-C(8)-H(8A)	120.3
C(7)-C(8)-H(8A)	120.3
C(8)-C(9)-C(4)	121.14(17)
C(8)-C(9)-H(9A)	119.4
C(4)-C(9)-H(9A)	119.4
C(1)-C(10)-H(10A)	109.5
C(1)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(1)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
N(2)-C(11)-C(12)	120.94(14)
N(2)-C(11)-H(11A)	119.5
C(12)-C(11)-H(11A)	119.5
C(13)-C(12)-C(17)	118.91(14)
C(13)-C(12)-C(11)	121.44(14)
C(17)-C(12)-C(11)	119.63(14)
O(2)-C(13)-C(14)	118.44(14)
O(2)-C(13)-C(12)	121.74(14)
C(14)-C(13)-C(12)	119.82(14)
C(15)-C(14)-C(13)	119.74(15)
C(15)-C(14)-H(14A)	120.1
C(13)-C(14)-H(14A)	120.1
C(14)-C(15)-C(16)	121.45(16)
C(14)-C(15)-H(15A)	119.3
C(16)-C(15)-H(15A)	119.3
C(17)-C(16)-C(15)	119.20(16)
C(17)-C(16)-H(16A)	120.4
C(15)-C(16)-H(16A)	120.4
C(16)-C(17)-C(12)	120.88(16)
C(16)-C(17)-H(17A)	119.6

C(12)-C(17)-H(17A)	119.6
C(2)-C(18)-H(18A)	109.5
C(2)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(2)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
O(3)-C(19)-O(4)	123.32(17)
O(3)-C(19)-C(1)	123.42(16)
O(4)-C(19)-C(1)	113.26(13)
O(4)-C(20)-H(20A)	109.5
O(4)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
O(4)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
O(5)-C(21)-O(6)	122.90(16)
O(5)-C(21)-C(2)	125.02(15)
O(6)-C(21)-C(2)	112.00(13)
O(6)-C(22)-H(22A)	109.5
O(6)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
O(6)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S-III-4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for d12336. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... \quad + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	46(1)	23(1)	43(1)	0(1)	-17(1)	-1(1)
O(2)	29(1)	38(1)	43(1)	-15(1)	-3(1)	5(1)
O(3)	74(1)	42(1)	128(2)	-39(1)	76(1)	-28(1)

O(4)	30(1)	22(1)	40(1)	5(1)	6(1)	3(1)
O(5)	147(2)	37(1)	97(1)	-25(1)	98(1)	-31(1)
O(6)	29(1)	22(1)	28(1)	1(1)	4(1)	-4(1)
N(1)	38(1)	21(1)	22(1)	-2(1)	6(1)	-4(1)
N(2)	30(1)	22(1)	27(1)	-3(1)	5(1)	-4(1)
C(1)	38(1)	22(1)	27(1)	-3(1)	10(1)	-8(1)
C(2)	31(1)	22(1)	30(1)	-6(1)	10(1)	-6(1)
C(3)	37(1)	22(1)	29(1)	2(1)	7(1)	2(1)
C(4)	30(1)	25(1)	22(1)	-1(1)	4(1)	0(1)
C(5)	31(1)	27(1)	24(1)	0(1)	1(1)	-1(1)
C(6)	40(1)	28(1)	32(1)	-3(1)	3(1)	-8(1)
C(7)	33(1)	46(1)	30(1)	-5(1)	4(1)	-14(1)
C(8)	30(1)	59(1)	39(1)	4(1)	-5(1)	-5(1)
C(9)	34(1)	39(1)	37(1)	5(1)	-1(1)	5(1)
C(10)	49(1)	30(1)	37(1)	-2(1)	20(1)	-8(1)
C(11)	28(1)	24(1)	27(1)	0(1)	8(1)	-1(1)
C(12)	28(1)	21(1)	25(1)	2(1)	5(1)	-3(1)
C(13)	28(1)	27(1)	27(1)	2(1)	0(1)	3(1)
C(14)	37(1)	29(1)	30(1)	-4(1)	-3(1)	6(1)
C(15)	42(1)	28(1)	28(1)	-2(1)	-4(1)	-3(1)
C(16)	30(1)	39(1)	29(1)	1(1)	-2(1)	-6(1)
C(17)	26(1)	34(1)	30(1)	2(1)	6(1)	-1(1)
C(18)	33(1)	28(1)	41(1)	-11(1)	15(1)	-7(1)
C(19)	39(1)	27(1)	30(1)	-8(1)	10(1)	-10(1)
C(20)	39(1)	32(1)	38(1)	2(1)	4(1)	11(1)
C(21)	38(1)	25(1)	32(1)	-5(1)	12(1)	-5(1)
C(22)	35(1)	29(1)	37(1)	5(1)	8(1)	-8(1)

Table S-III-5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å ^{2}x 10 ^{3}) for d12336.

	x	y	z	U(eq)
H(3A)	3110	5115	4003	35
H(6A)	2265	2335	3607	40
H(7A)	-322	2548	1631	44

H(8A)	-1303	3693	981	51
H(9A)	443	4633	2180	44
H(10A)	6428	5754	3838	57
H(10B)	8029	5165	4251	57
H(10C)	8098	5885	5327	57
H(11A)	10489	5308	9206	31
H(14A)	8228	7543	12765	39
H(15A)	11431	7686	13706	40
H(16A)	13786	6914	12820	40
H(17A)	12919	5996	10923	36
H(18A)	9485	4239	8254	50
H(18B)	9868	4773	6703	50
H(18C)	8403	4133	6372	50
H(20A)	3930	7368	6614	54
H(20B)	3643	6917	8341	54
H(20C)	2303	6774	6609	54
H(22A)	4701	2945	9281	50
H(22B)	3333	3606	9541	50
H(22C)	5130	3466	10894	50
H(1O)	5060(50)	3600(20)	5470(40)	100(12)
H(2O)	6700(30)	6265(13)	10000(30)	50(6)

Table S-III-6. Torsion angles [°] for d12336.

C(3)-N(1)-C(1)-C(10)	-78.11(19)
C(3)-N(1)-C(1)-C(19)	44.29(18)
C(3)-N(1)-C(1)-C(2)	161.11(13)
C(11)-N(2)-C(2)-C(18)	-13.0(2)
C(11)-N(2)-C(2)-C(21)	108.15(16)
C(11)-N(2)-C(2)-C(1)	-136.51(14)
N(1)-C(1)-C(2)-N(2)	-164.66(12)
C(10)-C(1)-C(2)-N(2)	75.59(16)
C(19)-C(1)-C(2)-N(2)	-47.48(15)
N(1)-C(1)-C(2)-C(18)	68.61(15)
C(10)-C(1)-C(2)-C(18)	-51.14(17)

C(19)-C(1)-C(2)-C(18)	-174.22(12)
N(1)-C(1)-C(2)-C(21)	-53.15(15)
C(10)-C(1)-C(2)-C(21)	-172.90(13)
C(19)-C(1)-C(2)-C(21)	64.03(15)
C(1)-N(1)-C(3)-C(4)	-177.38(13)
N(1)-C(3)-C(4)-C(9)	-179.96(15)
N(1)-C(3)-C(4)-C(5)	1.1(2)
C(9)-C(4)-C(5)-O(1)	-177.71(14)
C(3)-C(4)-C(5)-O(1)	1.2(2)
C(9)-C(4)-C(5)-C(6)	2.5(2)
C(3)-C(4)-C(5)-C(6)	-178.57(15)
O(1)-C(5)-C(6)-C(7)	179.45(16)
C(4)-C(5)-C(6)-C(7)	-0.8(2)
C(5)-C(6)-C(7)-C(8)	-1.7(3)
C(6)-C(7)-C(8)-C(9)	2.2(3)
C(7)-C(8)-C(9)-C(4)	-0.4(3)
C(5)-C(4)-C(9)-C(8)	-1.9(2)
C(3)-C(4)-C(9)-C(8)	179.12(16)
C(2)-N(2)-C(11)-C(12)	-173.55(13)
N(2)-C(11)-C(12)-C(13)	5.8(2)
N(2)-C(11)-C(12)-C(17)	-176.20(14)
C(17)-C(12)-C(13)-O(2)	-179.66(15)
C(11)-C(12)-C(13)-O(2)	-1.6(2)
C(17)-C(12)-C(13)-C(14)	0.2(2)
C(11)-C(12)-C(13)-C(14)	178.23(15)
O(2)-C(13)-C(14)-C(15)	-179.21(15)
C(12)-C(13)-C(14)-C(15)	1.0(2)
C(13)-C(14)-C(15)-C(16)	-1.3(3)
C(14)-C(15)-C(16)-C(17)	0.5(3)
C(15)-C(16)-C(17)-C(12)	0.6(2)
C(13)-C(12)-C(17)-C(16)	-1.0(2)
C(11)-C(12)-C(17)-C(16)	-179.07(14)
C(20)-O(4)-C(19)-O(3)	0.4(3)
C(20)-O(4)-C(19)-C(1)	-179.43(14)
N(1)-C(1)-C(19)-O(3)	35.3(2)
C(10)-C(1)-C(19)-O(3)	156.6(2)

C(2)-C(1)-C(19)-O(3)	-80.4(2)
N(1)-C(1)-C(19)-O(4)	-144.94(13)
C(10)-C(1)-C(19)-O(4)	-23.6(2)
C(2)-C(1)-C(19)-O(4)	99.40(15)
C(22)-O(6)-C(21)-O(5)	3.8(3)
C(22)-O(6)-C(21)-C(2)	-179.33(13)
N(2)-C(2)-C(21)-O(5)	20.0(3)
C(18)-C(2)-C(21)-O(5)	144.4(2)
C(1)-C(2)-C(21)-O(5)	-94.2(3)
N(2)-C(2)-C(21)-O(6)	-156.76(13)
C(18)-C(2)-C(21)-O(6)	-32.37(19)
C(1)-C(2)-C(21)-O(6)	89.11(16)

Symmetry transformations used to generate equivalent atoms:

Table S-III-7. Hydrogen bonds for d12336 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1O)...N(1)	0.86(4)	1.87(4)	2.6232(17)	146(3)
O(1)-H(1O)...O(6)	0.86(4)	2.48(3)	2.9914(17)	119(3)
O(2)-H(2O)...N(2)	0.86(3)	1.82(3)	2.6006(18)	151(2)

Symmetry transformations used to generate equivalent atoms:

국문초록

다이아자 코우프 자리바꿈 반응기법에 근거한 키랄 다이아민 기반 구조체들의 설계, 합성 및 응용

다이아자 코우프 자리바꿈 반응 기법(DCR) 에 근거한 합성법은 공명지원 수소결합 (RAHB) 을 그 추진력으로 하는 방법이며, 이는 다양한 C_2-대칭적 구조를 가지는 키랄 다이아민 뿐 아니라 비대칭의 키랄 다이아민을 합성하기 위한 유용한 방법으로 사용되어 왔다. 토론토 대학의 Jik Chin 교수에 의해서 이와 같은 자리바꿈 반응에 대한 연구가 소개된 후, 자리바꿈 반응 기법을 이용하여 합성된 다이아민을 기반으로 한 다양한 전이금속 촉매나 유기촉매의 개발 및 그 응용에 대한 연구가 더욱 활발히 진행되어 왔다. 그리고 자리바꿈 반응기법의 쉽고 효율적인 합성법을 바탕으로 다이아민을 포함하는 구조체에 입체적·구조적 변화나 다이아민의 전기적 다양성을 도입하여 촉매의 반응성 및 선택성을 향상시키고자 하는 연구가 많이 진행되어 왔다. 하지만, 현재까지 다이아자 코우프 자리바꿈 반응을 이용한 촉매 개발과 그 활성 향상에 대한 연구와는 달리, 생리적 활성을 띄는 물질의 주요 구조가 될 수 있는 다이아민을 포함한 골격 합성에 대한 연구의 예는 많이 알려지지

않은 실정이다.

본 연구는 다이아자 코우프 자리바꿈 반응기법에 의한 키랄 다이아민의 효율적 합성법에 근거하여, 다양한 키랄 구조체를 준비하기 위한 좋은 중간체로써 사용할 수 있는 비대칭적으로 치환기가 도입된 다이아민을 합성하고자 하였으며 이는 모계 키랄 다이아민과 각기 다른 알데하이드를 시작물질로 하여 이로부터 비대칭적으로 치환된 다이아민 구조체의 합성이 가능할 것이라고 예측하였다. 이와 같은 방법으로 생리적 활성을 띄는 물질들의 기본 골격구조에서 많이 확인할 수 있는 *trans*-3-아릴피페라진-2-카복실산 유도체와 γ,δ-다이아미노산 유도체들을 합성하였다. 그리고 기존에 금속이나 라디칼 개시인자를 이용한 반응으로 주로 합성된 아미노산의 이합체 구조를 모계 키랄 다이아민을 이용한 입체특이적 합성법을 통하여 합성하였으며, 이를 DFT 계산과 결정구조 분석법을 통하여 그 원리 및 입체적 특이성을 확인하였다. 추가적으로 다양하게 사용되고 있는 C_2-대칭적 구조를 지닌 다이아민의 광학적 순도를 확인하기 위해 라이보스와 아라비노스와 같은 단당류물질을 비대칭의 유도체 (Chiral derivatizing agent) 로써 사용하는 연구를 진행하였다.